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THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

## February, 1954

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PUBLISHED MONTHLY
THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland
*Made in United States of America*

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# BULLETIN OF

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*Subscription price.* In the United States and its possessions $8.00 per year. In Canada $8.25 per year; in foreign countries $8.50 per year. Single numbers, $1.00.

*New subscriptions and renewals* are entered to begin with the first issue of the current year. Subscribers in the United States are hereby notified that missing numbers cannot be replaced unless notification of loss is received in this office within 1 month following publication of the missing number; foreign subscribers 6 months.

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BALTIMORE-18, MARYLAND, U. S. A.

Entered as second class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

# HYPERTENSION RESULTING FROM UNILATERAL RENAL VASCULAR DISEASE AND ITS RELIEF BY NEPHRECTOMY

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Received for publication December 11, 1953

## INTRODUCTION

In 1934 Goldblatt (1) demonstrated that hypertension can be produced experimentally in some dogs by reduction in the arterial blood supply to one kidney. Others (2) have shown that unilateral arterial constriction usually causes persisting hypertension in the rat and rabbit. These observations have led to widespread speculation whether a similar mechanism might be responsible for some instances of hypertension in man. This report concerns six patients apparently relieved of their severe hypertension by unilateral nephrectomy, in all of whom there was evidence of reduced arterial blood supply to either the whole or substantial parts of the offending kidney. It is believed that the data from these cases add strong evidence to the theory that relatively ischemic renal tissue elaborates an hypertensive agent, and that the data also suggest methods for recognizing those hypertensive patients who are amenable to relief by nephrectomy.

## REPORT OF CASES

*Case 1* (J. W. C.—JHH #117186).† The first patient of this series was restored from severe hypertension to normal cardiovascular status despite an extraordinary series of diagnostic errors. A white married executive of 31 years entered The Johns Hopkins Hospital in August, 1937 under the care of Dr. C. Holmes Boyd because of hypertension. There was no known history of hypertension in his family. Periodic headaches of migrainous type had been present since the age of 10. He had passed a life insurance examination in 1931. Four years prior to his admission here the patient had an episode of left lower quadrant pain which lasted for two weeks and was diagnosed as "spastic colon." Eleven weeks prior to admission a pain of similar character occurred, and for three weeks he was studied at his home with "negative findings, including roentgenograms." The pain then shifted to the right lower quadrant and vomiting supervened. An appendectomy was performed under spinal anesthesia. (Patient was told that the appendix was not diseased.) Blood pressure was normal. On the fifth post-operative day the patient experienced headache and very severe pains in the arms. A blood pressure of 180 mm. Hg was noted. The pains in the arms were accompanied by whiteness of the hands so that the patient would hang his hands over the bed "to improve the circulation." These manifestations continued for about three weeks. One month prior to admission (four weeks after appendectomy) vision became reduced in

*R. S. McLaughlin Foundation Travelling Fellow.

†This case has been previously reported (3).

the right eye. Headaches persisted. Nocturia appeared two or three times each night. There had been a weight loss of 30 lbs. over the two month period prior to admission here.

*Examination:* The temperature was 98.6°F., pulse 100 and the blood pressure 200/120. Weight loss was evident. Dr. Frank B. Walsh reported "vision RE 20/30, LE 20/15. Fields show paracentral scotoma in LE; slightly enlarged blind spots. RE: Media clear. Disc shows blurred margins. There is retinal edema, particularly in the macula where there is an exudate typical of hypertensive disease. There are two or three linear hemorrhages in the region. No exudates elsewhere. Vessels show marked attenuation near the disc. Peripheral variations in caliber are also seen. LE: Pupil dilates badly. The disc is similar to that of RE. In the macular region there is a large patch of exudate toward the disc. Impression: Hypertensive retinopathy with papilloedema." The tonsils had been removed but tags remained which were infected and contained small pustules. The heart was not enlarged. The second aortic sound was accentuated; no murmurs were present. Abdominal, genital and neurological examinations revealed no abnormalities. During the pre-operative studies, blood pressure readings ranged between 205/135 and 155/115 mm. Hg.

*Laboratory data:* During water restriction test the specific gravity of the urine rose to 1.017. There was a trace of albumen and the sediment contained a few WBC and casts. Phenolsulphonphthalein excretion was 70 per cent in two hours. The hemoglobin was 14.6 gm. per 100 cc., hematocrit 43 per cent, the white cell count was 6,250 with normal differential count. The sedimentation rate was 25 mm. in an hour (Wintrobe). The serological test for syphilis was negative. The non-protein nitrogen was 26 mg., and the fasting blood sugar was 70 mg. per 100 cc. Stool examination revealed no abnormalities.

The possibility of a pheochromocytoma was raised and one of us (J. E. H.) was asked to see the patient in consultation. It was believed on clinical grounds that no such lesion was present but combined perirenal air injection and intravenous pyelograms were interpreted as suggesting a mass in the left adrenal area, *with normal kidneys.*

It was decided, therefore, to explore the adrenals, the fashion at the time being bilateral exploration from the rear. On September 3, 1937, Drs. Lloyd Lewis and H. H. Young performed the operation. The operation on the left finished first, the adrenal tumor proving to be mythical. The right adrenal also appeared to be normal; but at this time the interne became fatigued and let his retractor slip, exposing the upper pole of the right kidney which had a curious yellow appearance thought to indicate malignant tumor. Nephrectomy was carried out on this basis. Postoperative convalescence was uneventful, with a gradual fall in blood pressure such that at discharge three and one-half weeks later the reading was 150/100. Headaches and blurring of vision disappeared. Postoperative urine revealed no albumen or abnormal elements in the sediment. The appearance of the optic fundi had not changed when the patient left the hospital on September 27, 1937. In November, 1937 the family physician found the blood pressure 140/100, and in December, 1937 it was 140/90.

The patient was seen next by Dr. Boyd* on May 24, 1938 at which time the patient reported his health to have been good. General physical examination was normal. The blood pressure was 118/82. During a concentration test urine specific gravity was reported 1.032. Dr. Frank B. Walsh's note of this date reads as follows: "RE disc blurred above and below, not to the sides. In macular region are flat hard white exudates. These are not seen elsewhere in fundus—only a small number are noted. There are no hemorrhages. The vessels are remarkable in that they are normal except on the disc. The large vessels are within normal limits; the small vessels around the disc are narrowed. One with "cattle-tracking" appear-

* We are deeply grateful to Dr. Boyd for permission to use his office records for follow-up notes on this patient.

ance is probably a vessel brought into view because of compensatory circulation. LE: The disc shows web-like glial tissue, no doubt arising from previous papilledema. The macula is clear save for one tiny spot of hard exudate. Peripheral fundus clear. Vessels are as in RE. No hemorrhages. Vision 20/15 in both eyes."

On July 16, 1948, Dr. Walsh's note reads: "There are a few tiny vitreous opacities in the right eye; none seen in left. Right disc is normal. To the nasal side of the left disc there is some fibrous tissue which undoubtedly is developmental. In the right macula there are a few drusens. There are no hemorrhages or exudates. The retinal arteries would pass as normal. On close inspection there are occasional areas of increased light streaking. The calibre of the arteries is uniform and there are no changes in the A-V crossings."

Between the years 1938 and 1952 patient was seen periodically by Dr. Boyd. He complained of a wide variety of minor symptoms usually associated with life situations. In 1946 there was a momentary episode of right hemiparesis and this has been followed by periodically recurring sensory Jacksonian attacks involving the right facial area and right side of tongue. These were interpreted by Dr. J. W. Magladery as "due to an irritative lesion in the parietal cortex, probably due to softening and subsequent scarring from vascular disease." Except for a single reading of blood pressure 190/130 recorded elsewhere immediately following the momentary hemiparesis, blood pressure readings have always been normal, 140/90 being the highest. In 1939 the urine was found to be entirely normal; since then there has always been +albumen reported without other abnormal urinary findings. In 1952 urine could be concentrated to 1.024.

*Pathological findings:* Over the upper pole perirenal tissues were adherent to the kidney capsule. The kidney weighed 138 grams. A yellow depressed area 2 cm. in width and typical of an infarct was seen in the upper pole. Surrounding this infarct and involving the upper half of the kidney, there was a ½ to 1 cm. depression of the cortical tissue measuring 3½ by 5½ cm. The lower pole was normal, as were the calyces and pelvis. Microscopic sections have been lost but the descriptions available indicate that the infarct was surrounded by broad areas of renal tubular atrophy with preservation of glomeruli. No lesions were seen in the lower pole or in the pelvis.

*Summary:* A male of 31 had abdominal pain for which a normal appendix was removed. Five days later hypertension appeared and progressed steadily for three months. Severe retinopathy was present. Intravenous pyelography was normal. During bilateral exploration for a supposed pheochromocytoma, a yellowish mass was found in the right kidney and this kidney was removed. The mass proved to be an infarct. After nephrectomy B. P. fell gradually and for the past 15 years he has been normotensive.

*Case 2* (P. C.—JHH #503826).* A 45-year-old physician was admitted to the Johns Hopkins Hospital on June 10, 1949 on the surgical service of Dr. William Grose because of acute abdominal pain. His previous health had been good, and the blood pressure had never been elevated.

Six days before admission he had had sore throat with tonsillar exudate and fever, for which he had administered penicillin to himself. There was improvement in malaise and the fever fell by lysis. He resumed work and felt well except for slight fatigue until 1 p.m. on the day of admission, when, during lunch, there appeared in the right lower quadrant an aching pain severe enough to cause him to leave the table. He passed a soft stool without relief. He lay on the lavatory floor for 10 minutes and the pain now radiated to the costovertebral angle. The severe discomfort gradually abated, and the patient went to a meeting where at 3:30 p.m. a colleague found his abdomen soft and free of tenderness. At 4 p.m.

* This case was previously reported by Arnold, Goodwin and Colston (4).

urine was examined and reported normal, and the white blood cell count (reported later) was 22,000 with 82 per cent polymorphonuclear cells. He started to drive to his home, but bumps on the road were painful. At 5 p.m. he stopped the car and noted rebound tenderness to his own touch in the right lower quadrant. This caused him to turn around and return to Baltimore where he entered the hospital at 7 p.m. By the time of admission he felt quite well again.

*Physical examination* (Dr. William Grose): The temperature was 99°F. by mouth and the blood pressure was 130/70. The tonsils were red, and there was mucopurulent discharge in the pharynx. The heart and lungs were normal. The abdomen was soft with deep palpation permitted everywhere, except that low and far lateral on the right there was the slightest tenderness which was neither constant nor severe. There was an equivocally positive psoas sign. Examination of external genitalia and rectum was normal. There was no local or general lymphadenopathy. The white cell count was 14,000. The urinalysis showed no albumen and 20–30 white cells per high power field in the spun sediment.

Dr. Grose's impression was "this illness fits neither pyelitis (suggested by the second urine specimen) nor appendicitis. The onset following a severe upper respiratory infection (probably a streptococcal throat) very much suggests mesenteric adenitis. My first inclination is to operate despite the apparently falling white count and the apparently newly appearing pyuria."

Operation was performed through a right McBurney incision and a normal appendix was removed. No satisfactory explanation for the illness was found. Postoperative recovery seemed uncomplicated except for daily elevation of the temperature to 100° by mouth. Gall bladder and gastrointestinal X-rays and electrocardiogram were normal. An excretory urogram revealed no abnormality. Urine culture showed a growth of staphylococcus albus. The single urinalysis in the postoperative record revealed no albumen or sugar. There were 5–15 white cells and 3–5 red cells per high power field in the sediment and no casts. Patient was discharged from the hospital on June 17th, one week after operation, with the diagnosis of "abdominal pain, unclassified."

He was readmitted to the hospital June 29th to July 7th because mild right flank pain and low grade fever had been present since the previous discharge. Patient had examined his own urine and had noted albumen with varying numbers of red and white cells. While in the hospital, the temperature remained normal but the blood pressure was noted to fluctuate between 150/85 and 200/100. Eye grounds were normal except for some irregularity and spasticity of the retinal arterioles. A soft apical systolic murmur was present. Repeated urinalyses revealed 0 to trace of albumen, occasional white cells, no red cells and rare cellular and hyaline casts. The blood non-protein nitrogen was 32 mg. per 100 cc. During a Fishberg test the urine was concentrated to 1.020. The phenolsulphonphthalein excretion was 20 per cent in 15 minutes and 55 per cent in two hours. Diagnosis at discharge was "glomerulonephritis, acute."

The patient's third admission to the hospital was August 8, 1949. Hypertension and intermittent albuminuria had continued and his general health was deteriorating rapidly. He complained of chronic fatigue, persistent headaches and anorexia. There had been a weight loss of 30 pounds in the preceding two months. Mild dyspnea and palpitation resulted from exertion. During this admission blood pressure readings ranged from 195/120 to 220/130. Examination of the fundus revealed bilateral papilloedema with hemorrhages and exudates. In the hospital the papilloedema increased and the patient could not read newspaper headlines. The heart was not enlarged; the second aortic sound was moderately accentuated. The urine was acid. Its specific gravity rose to 1.021 during a Fishberg concentration test. It always contained a trace of albumen and in the sediment a few white

cells were noted. There were intermittent showers of red cells, and no casts were reported. Blood non-protein nitrogen determinations were normal. Under amytal sedation the lowest blood pressure reading was 175/110. A benzodioxane test was negative.

On August 15th the patient was seen in consultation by one of us (J. E. H.). In view of the marked similarities to Case 1, the possibility of renal infarction was discussed with the patient and exploration of the right kidney was agreed upon. Intravenous pyelography was repeated and "shows no change during the past two months except for the size of the kidney shadows. The left kidney appears to have increased slightly. There appears to be a real decrease in the size of the right kidney which now measures 11.5 cm. in length, whereas two months ago the length was greater by 1 cm. The transverse diameter of the kidney shows a decrease of approximately 0.5 cm."

On August 24th a right nephrectomy was performed by Dr. J. A. C. Colston. On the first postoperative day, the blood pressure fell to 140/80 and thereafter the highest reading was 180/110 with an average of 160/100. There were no postoperative complications. Headache disappeared entirely; vision improved so that on discharge 10 days after nephrectomy he could read the newspaper without difficulty.

Following discharge from the hospital, daily blood pressure readings were taken at home. On September 10th the reading was 150/90, and all but occasional subsequent readings were below this level.

Patient was next seen on November 18, 1949. Symptomatically he had been entirely well. There had been a weight gain of 30 lbs. which restored him to his usual weight. The eye grounds now revealed no abnormalities. The blood pressure was 160/110 sitting, 150/90 recumbent. The pulse was 82. The only urinary abnormality was a faint trace of albumen.

On May 3, 1951 the patient was seen again. He reported excellent general health. Dr. William C. Owens, ophthalmological consultant who saw the patient prior to operation, could find no evidence of the previous hypertensive retinopathy. Blood pressure 150/90. The examining physician's (J. E. H.) note reads: "The patient is clearly sensitized to the blood pressure cuff for every time he is approached with one he feels his tension mounting. His wife, on frequent determinations made at home, finds his blood pressure 120/70." Urinalysis was entirely normal, with a specific gravity 1.023. Phenolsulphonphthalein excretion was 30 per cent in 15 minutes. The electrocardiogram was normal.

In June, 1952 the patient was still feeling entirely well and carrying on active practice. Examinations were entirely normal except that blood pressure was 160/100 sitting. The consultant noted "I still feel blood pressure elevations are due to emotional sensitization to having his blood pressure taken. He tells me he could feel his pulse rate increasing while thinking about the examination on the way to Baltimore."

In May, 1953 the blood pressure was found to be "normal" at an Army Induction Center.

*Pathological findings:* This kidney (S. P. 49-3422) was about one-half normal size and weighed 90 grams (Fig. 1). There were small adhesions to the capsule which stripped from the cortical surface with slight increase of resistance from small foci of scarring. One artery entered the upper pole as an aberrant vessel (Fig. 1). A major renal artery divided in the renal hilus into three branches which supplied the lower two-thirds of the kidney. The upper pole of the kidney appeared normal while the lower two-thirds was clearly atrophied with a sharp line of demarcation between normal and atrophied cortex (Fig. 1). On cut surface, the cortex of the upper pole measured 5 to 6 mm. in thickness, that of the atrophied zone, 2 to 3 mm. A small shallow infarct was seen in the lower pole, several mm. in depth. There was an increase of peripelvic fat. Microscopic sections of the largest renal artery revealed severe intimal proliferation (Fig. 2). The renal parenchyma of the upper pole was normal. That of the entire lower two-thirds of the kidney showed severe atrophy of most of the con-

voluted tubules. This atrophy was not perfectly homogeneous for an occasional tubule seemed normal. There was a relatively sharp line of demarcation between normal and atrophic tubules (Figs. 3 and 4). Slight round cell infiltration of the atrophied zone was present. The glomeruli were normal throughout, although in the atrophied zone the glomeruli were found to be relatively more numerous in a given area, doubtless the result of the atrophy of intervening tubules. A small infarct with hyalinizing tubules and glomeruli, compatible with six weeks or two months duration, was present. Hyaline arteriolosclerosis was seen in both atrophic and normal portions of the kidney. The pelvis and calyces were normal.

*Summary:* A 45-year-old physician developed abdominal pain six days after a streptococcal sore throat. Appendectomy was performed but the appendix was normal. Hypertension was first noted 19 days after appendectomy, and progressed rapidly. Two months after appendectomy severe retinopathy was present and the patient's condition was deteriorating. Intravenous pyelography was interpreted as normal. Because of similarity to Case 1, the right kidney was removed and found to contain a small infarct and a large area of renal atrophy. Blood pressure fell gradually and eyes improved rapidly. He has felt well since; eye grounds have completely cleared and, though still somewhat labile, his blood pressure is usually normal, the highest reading recorded being 160/100.

*Case 3* (M. G. P.—JHH #590319). A 39-year-old merchant was admitted to The Johns Hopkins Hospital November 12, 1951 because of recent development of headache, fatigue and dyspnea. His mother died at age 63 from heart trouble. One brother suffered a coronary occlusion at age 55.

The patient had been seen (by J. E. H.) in 1937 because the blood pressure had been found slightly elevated during an examination for life insurance. There were no symptoms. He showed evidence of vasomotor instability. Blood pressure was 150–155/100–105, but physical findings were otherwise normal. The patient appeared to be of introspective and worrying nature and reacted with alarm whenever his blood pressure was determined. He was reassured and no therapy was prescribed for him. Subsequently he was told that his blood pressure was normal and he had been granted life insurance on two occasions, the last being in June, 1951.

In July, 1949 the patient had been seen by Dr. E. Cowles Andrus with symptoms and signs of subdeltoid bursitis. Blood pressure at that time was 155–165/100–110. Electrocardiogram was normal, and there was no change in the tracing after a Master test.

Six weeks prior to hospital admission the patient began to experience dull bitemporal headaches and mild exertional dyspnea. He went on a 5,000 mile automobile trip for his vacation, during which he began to have episodes of paroxysmal nocturnal dyspnea and finally was forced to sleep sitting up. On his return, October 23rd, he again consulted Dr. Andrus who found blood pressure 185/125 with signs of early congestive heart failure. Electrocardiogram showed left ventricular strain. Rest, digitoxin and salt restriction were prescribed with some improvement; but he was admitted to the hospital by Dr. Andrus for further study.

*Physical examination:* The temperature was 98.6°F. The blood pressure was 200/130. There were no signs of heart failure. Venous pressure was 105 mm. of water. The liver was palpable on deep inspiration. Retinal arterioles showed increased light reflex and some a-v compression but there were no exudates, hemorrhages or papilloedema. The urine concentrated to 1.022, sugar and albumen were absent, and the sediment contained only occasional white cells and hyaline and granular casts. There was no anemia. The white cell count was 12,000. The differential count was normal, and the sedimentation rate was 7 mm. in one hour. Phenolsulphonphthalein excretion was 62 per cent in two hours. The non-protein nitrogen was 37 mg. per 100 cc., serum $CO_2$ was 30.4 meq., and Cl was 98 meq. per liter.

Blood pressure ranged between 200/130 and 140/110. The hypertension persisted under sodium amytal sedation, the lowest reading being 165/115. Intravenous pyelogram revealed no excretion of opaque medium from the left kidney. On cystoscopic examination by Dr. Walter Denny there was clear urine coming from the right ureter, none from the left. Retrograde pyelogram showed both tracts well outlined and of normal architecture. The left kidney was well defined and measured 11.5 cm.; the right kidney measured 15 cm. The patient's *severe* hypertension appeared to be of recent origin and the renal findings made it seem likely that the non-functioning kidney was etiologically important.

At noon on January 4, 1952 left nephrectomy was performed by Dr. Hugh J. Hewett The operator noted numerous adhesions of the perirenal fascia, and he remarked that the kidney surface was dark mahogany in color instead of the usual reddish brown. Pulsation could be felt in the renal pedicle, but the artery seemed of smaller than average calibre.

Postoperative course was smooth and uncomplicated. At 7 p.m. on the day of operation the blood pressure was 130/80. Thereafter, until discharge on January 12th, the blood pressure varied between 130/90 and 150/100.

On February 15, 1952 patient was seen again by Dr. Andrus. In the interval there had been no headaches or symptoms of heart failure, and blood pressure taken on several occasions by the family physician had been 135/80. General examination was entirely normal. Blood pressure was 140/90. Four months after operation the blood pressure was 125/85, and the optic fundi were normal.

Patient was last seen October 1, 1953. He had felt well, worked hard and his exercise tolerance was normal. Blood pressure readings were 168/108 and after 10 minutes rest, 145/100. He admitted that on the way to the hospital the thought of having his blood pressure taken had made him feel quite tense.

*Pathological findings:* This kidney (S. P. 52-44) was recorded as weighing 140 grams. The capsule stripped with ease, leaving a very finely granular surface. There was an increase in peripelvic fat. The calyces and pelvis were normal. In the hilum of the kidney a number of small renal arteries entered the kidney but the main artery was not present. The cortex did not seem narrow. Histologically, although superficial study suggested a normal kidney, it was clear that a remarkable diffuse tubular atrophy had occurred, leaving almost all of the convoluted tubules as narrow pale-stained structures resembling distal convoluted or even small collecting tubules (Figs. 5 and 6). A very rare normal appearing proximal convoluted tubule was noted. The glomeruli were all essentially normal. In each low-power microscopic field, many more glomeruli were observed than in a normal control kidney. Counts were made and it was noted that while the average in 100 fields counted was seven glomeruli per low-power field in several normal kidneys, 12 per low-power field were counted in this kidney. This was obviously a result of condensation of renal tissue due to atrophy of convoluted tubules. No arterio- or arteriolosclerosis was observed. A very slight round cell infiltration of the cortex was found but no suggestion that this was a pyelonephritis was seen and the pelvic and calyceal tissues were normal.

*Summary:* A 39-year-old merchant had had labile blood pressure for 14 years (highest reading 155/105) but had been asymptomatic. He rather suddenly developed headaches, exertional dyspnea and the blood pressure was found markedly elevated with accompanying acute cardiac failure. Intravenous pyelography revealed no excretion of dye by the left kidney; retrograde studies showed no urine coming from the left ureter but normal renal architecture. The left kidney was removed and showed general atrophy of the renal tubular epithelium. The blood pressure fell and was normal by the seventh postoperative day. In the ensuing 21 months the patient has felt well, but he continues to have mild hypertension under stress.

*Case 4* (I. N. JHH #629194). A 37-year-old tobacco buyer was admitted to The Johns Hopkins Hospital on the service of Dr. J. A. C. Colston on January 21, 1953 for investigation of his hypertension.

His father had had three operations for renal calculi and a nephrectomy. His death occurred at age 54 from a ruptured aorta, but his blood pressure is not known to have been elevated. The patient's mother, aged 87, had recently developed hypertension.

The patient's past health had been good except for three episodes of right-sided abdominal pain interpreted as ureteral colic.* The first of these, which he remembered only vaguely, occurred at the age of 12, lasted two to three days, and subsided spontaneously. In 1939 there was recurrence of a similar pain without gross hematuria. During this episode, which was never severely painful and lasted about one week, he does not recall passage of any calculi. In July, 1952 the patient experienced his third attack, which was more severe than the previous ones and resulted in hospitalization. Urinalysis revealed microscopic hematuria and pyuria but no stone was passed. Flat film and intravenous pyelogram were normal. Blood pressure was normal during this hospitalization. After recovery from this attack the patient donated blood to the Red Cross and no comment was made at this time when his blood pressure was taken.

In November, 1952 he began to have dull headaches and consulted a physician who told him his blood pressure was slightly elevated. During the next two months frequent readings were taken and hypertension was observed to be rapidly progressing. Two weeks prior to admission it was found to be 240/140. Under amytal sedation test performed by his physician, Dr. A. O. Wooddy of La Plata, Maryland, the blood pressure fell to 140/100.

*Physical examination:* The temperature was 99°F. by mouth, pulse 76, and blood pressure 220/120. He looked well, though the hair was gray and the appearance was that of a man more than 37 years old. Positive findings were: the second aortic sound was loud, and there was a faint apical systolic murmur without gallop rhythm. There was retinal arteriosclerosis with pronounced nicking at the a-v crossings. Retinal arteries were not narrowed but many of these vessels had a coppery appearance. There were patches of hemorrhage and exudate in both retinae, but the discs were normal. The urine was acid, with a specific gravity of 1.020, +albumen, 0 sugar, 1–2 red cells and 3–5 white cells per high-power field in the spun sediment. There were no abnormalities in the blood morphology. Blood non-protein nitrogen was 32 mg. and sugar 92 mg. per 100 cc. The serum calcium was 11.0 and phosphorus 3.4 mg. per 100 cc. The serum $CO_2$ was 28.7 and Cl 95.0 meq. per liter. The electrocardiogram was normal except for slight depression of the S-T segment in V5. Chest roentgenogram disclosed no cardiac enlargement or lung abnormality. The benzodioxane test was negative. Intravenous pyelogram disclosed prompt bilateral excretion. Although concentration of the opaque medium was quite low, the upper urinary tracts were interpreted to be within normal limits.

The possibility of a unilateral renal lesion as the cause of the hypertension was suspected from the history. On comparison with pyelograms made in July, 1952 (kindly furnished us by Dr. E. J. McDonald of Washington, D. C.) it was believed that the right kidney had shrunk about ½ inch in length. Bilateral simultaneous catheterization of the ureters was performed by Dr. Colston. The volume of urine from the right ureter in ½ hour was 10 cc., whereas 100 cc. was obtained from the left. The sodium concentration in the urine from the right side was 11 meq. per liter, in that from the left side 19 meq. per liter. Abdominal aortography was performed (Fig. 7), and this disclosed a definite localized constriction of the right

* At an examination on March 26, 1953 the patient recalled that since age 18 he had frequently experienced nagging discomfort in the right loin, especially after a long car ride or at the movies. He said this discomfort had been absent since nephrectomy.

main renal artery close to its origin from the aorta. Distal to this point, the right renal artery appeared normal, and there was no gross diminution in the opacity of this vessel or the kidney parenchyma as compared with the opposite side. On January 28, 1953 right nephrectomy was performed by Dr. Colston. Following operation there was a rapid fall in blood pressure. On return from the operating room blood pressure was 170/110. Two hours later it was 145/80 and from the next day onward the highest reading recorded was 160/88. Headaches promptly disappeared, and there was definite evidence of clearing of the retinopathy when the patient was discharged on the 13th postoperative day.

On February 24, 1953 the patient reported that he had been feeling entirely well. Blood pressure was 130/90 sitting. Hemorrhages and exudate had almost completely disappeared from the retinae. On March 26, 1953 blood pressure was 140/95 recumbent on the first reading; after five minutes 120/85. Urine examination was normal.

His latest examination was on October 10, 1953 at which time he was feeling excellent and was entirely symptom free. Resting blood pressure was 138/86. Eye grounds were normal.

*Pathological findings:* A kidney (S. P. 53-416) which appeared entirely normal weighed 161 grams. The capsule stripped with ease, leaving a smooth surface. The available arteries were normal as were the calyces and pelves. The cut surfaces revealed a normal cortical width, with normal markings. Microscopically the only significant change noted was an apparent prominence of the juxtaglomerular apparatus. These bodies were found with relative ease and were often quite large (Fig. 8). Special granule stains have not been done. The proximal convoluted tubules were entirely normal and glomeruli appeared normal. The brush border of the proximal convoluted tubules stained normally with periodic acid-Schiff staining. No inflammation was present in the parenchyma, or in the pelvic or calyceal tissues.

*Summary:* A 37-year-old male had right-sided abdominal pain interpreted as renal colic. There was microscopic hematuria and pyuria but flat film and intravenous pyelography were normal. His blood pressure was then and had always been normal. Four months later headaches developed and blood pressure was found moderately elevated. His physician noted rapid progression of the hypertension over the next two months, with appearance of retinal exudates and hemorrhages. Intravenous pyelography was again interpreted as normal. Simultaneous ureteral catheterizations yielded a lesser flow of urine from the right kidney and lower sodium concentration was present in this urine than in that from the other side. Arteriography disclosed a constriction of the right main renal artery. After right nephrectomy there was rapid fall in blood pressure and the patient has remained well and normotensive for the subsequent nine months.

*Case 5* (J. D. HLH #B-1117).* A 4-year-old colored boy was admitted to the Harriet Lane Home of The Johns Hopkins Hospital on March 27, 1953 because of a generalized convulsion. There was no family history of epilepsy or hypertension. At age 22 months the patient had been admitted to the University of Maryland Hospital suffering with lobar pneumonia. While there he developed a right hemiplegia. Nine months prior to admission he had a clonic and tonic convulsion for which he was admitted to the Provident Hospital for observation. Blood pressure at that time is not known. He was symptomless until the day of admission when he had another generalized convulsion and was brought to the accident ward. Blood pressure was found to be 200/160. During hospital study the blood pressure was usually 200/140, some readings were as high as 200/170. The signs of an old right hemiplegia were present. Urine could be concentrated to 1.028; some specimens showed a trace of al-

*This patient was seen in consultation with Dr. Lawson Wilkins and members of the Harriet Lane house staff. The case will be reported in detail by members of the Pediatric staff.

bumen; sediment was always normal. Retinal vessels were tortuous and constricted, but papilloedema, hemorrhages and exudates were absent. Intravenous pyelograms and retrograde right pyelogram were normal (left ureter could not be catheterized owing to technical difficulties). Benzodioxane and Regitin® tests negative. In a retrograde aortogram (via catheter introduced through femoral artery) no main renal artery could be demonstrated on the left side (Fig. 10). However, the opaque medium did outline the left kidney and a tortuous left ureteral artery was visualized, suggesting retrograde filling of the renal arterial tree through this vessel (Fig. 11). On May 1, 1953 left nephrectomy was performed by Dr. John Grayhack. A small tumor mass, identified by frozen section as a ganglioneuroma (Fig. 9), was found lying in close approximation to the left renal pedicle. The tumor and the left kidney were removed. After operation the blood pressure fell gradually and on the 14th postoperative day was 140/70. On June 19, 1953 the patient was seen in the out-patient department with a respiratory infection. Blood pressure was 125/80. He was last seen on October 22, 1953. He was fully active and symptom free. The blood pressure was 130/90 seated and 128/72 recumbent. The retinal vessels still showed tortuosity but the calibre was normal and there was no a.v. nicking.

*Pathological findings:* The first portion of the specimen received (S. P. 53-1963) was a nonencapsulated rubbery mass of tissue measuring 2 by 3½ by 2 cm. On cutting, pale yellow nodules bulged above the surrounding strands of gray connective tissue. The second specimen was a left kidney weighing 60 gm. (normal 65 gm.) and measuring 8 cm. from pole to pole. A single major renal artery and its branches were grossly normal as were the renal veins, the ureter and the pelvis. The capsule stripped with ease and the cortical surface was only very finely granular. The cut surface showed normal cortical and medullary markings. The calyces and papillae were normal. Microscopically the tumor was a typical well differentiated ganglioneuroma. Sections of the kidney showed that most glomeruli were normal. Occasionally the cytoplasm of the endothelial cells was prominent and such glomeruli appeared relatively avascular. Juxtaglomerular bodies were often seen but were not appreciably enlarged. Foci of atrophy of convoluted tubules were small but definite and one small subcortical scar with hyaline glomeruli was noted. It was thought to be a tiny healed infarct. Slight to moderate focal round cell accumulation was seen. Hyaline arteriosclerosis was occasionally found, both of interstitial and of glomerular arterioles. The intrarenal arteries were normal. The pelvic and calyceal tissues were also normal.

*Case 6* (E. C. G., Hospital for the Women of Maryland #52-435-2)*. The patient was a 54-year-old white housewife who was admitted to the Women's Hospital on April 22, 1953 complaining of abdominal pain and vomiting of several hours duration. Her family history was noncontributory. There had been two normal pregnancies at 16 and 18. A tubo-ovarian abscess had been drained in 1933. Cholecystectomy had been performed some years previously. Menopause occurred in 1937. The patient had been told by physicians for several years that her blood pressure was elevated, but stated also that in 1935 and again in 1947 she had been treated for low blood pressure. Her average weight had been 145 pounds, but there had been a loss of 10 pounds during the three months prior to admission. On April 22nd the patient suddenly developed right sided abdominal pain and vomiting. A physician administered morphine and referred her to the hospital with the impression that she had either a perforated peptic ulcer or a common duct stone. Initial blood pressure 210/110. The urine was negative for albumen and sugar. There were no abnormal elements in the sediment. On April 22nd a bilateral sympathetic block from $T_6$ to $T_9$ was performed under the impression that the patient was suffering from acute pancreatitis. However, the subse-

* This patient was seen in consultation with Drs. George S. Watson, F. M. Dugan and H. Reissman, to whom we are indebted for the privilege of including her case in this report.

quent course showed an intestinal obstruction to be present and laparotomy was performed. About 8 cm. from the ileocecal valve there was a loop of gangrenous ileum 12 inches in length incarcerated beneath an old adhesion. The loop was resected and end to end anastomosis carried out. She was discharged on May 5, 1953. Postoperatively there were three recordings of the blood pressure—160/95, 200/95 and 210/95.

After discharge the patient seemed well for a few days but then began to have right sided headaches. Her physician treated her with pills for hypertension. She vomited frequently, and lost 10 pounds in weight. On May 25th mental confusion became evident, and the patient was readmitted to the hospital.

*Physical examination:* Temperature normal, blood pressure 225/120. Patient was disoriented and resisted examination. There was profuse sweating. Pupils were dilated and did not react to light. Fundi showed "grade 3 hypertensive changes." Hemorrhages and exudates were present bilaterally, and the left disc margins were blurred. The patient was believed to be suffering from hypertensive encephalopathy.

The urine showed ++++ albumen, 0 sugar and +++ acetone. The sediment showed 10–15 white cells and an occasional cast per high-power field. The hemoglobin was 13.8 gm. per 100 cc. The white cell count was 24,000 of which 86% were polymorphonuclear cells. The blood sugar was 107 mg., urea 41 mg. and creatinine 3.2 mg. per 100 cc. Serum chloride was 92, $CO_2$ 26.8, potassium 2.7 and sodium 135 meq. per liter. Teleoroentgenogram showed normal cardiac size.

A generalized convulsion occurred on May 28th. On combined therapy of fluid administration, hexamethonium chloride and Rauwolfia serpentina, the patient gradually improved so that on June 20th she was oriented, eating and feeling reasonably well, though highly nervous and excitable. Coincidentally albuminuria decreased to one plus.

Phenolsulphonphthalein excretion was 20 per cent in two hours on June 9th, but had risen to 50 per cent in two hours on June 25th.

On June 2nd intravenous pyelogram disclosed the left kidney to be normal; the right kidney failed to excrete any opaque medium.

On June 16th intravenous pyelography was repeated: "Left collecting system remains the same. There is now definite evidence of function on the right, but the right calyceal system is very delicate and consequently poorly defined in its entirety."

On June 18th a right retrograde pyelogram was made—"right calyceal system is within normal limits." No urine appeared from the right ureter.

On May 30th, 16 mg. benzodioxane were administered intravenously. Baseline blood pressure was 235/150. After one minute the pressure had fallen to 200/150 and after three minutes was 100/?, and pulse 150. The skin was cold and clammy and the patient vomited. Over the next five minutes, without medication, blood pressure rose gradually to 240/140. It is not known whether any drugs had been administered to the patient prior to the performance of the benzodioxane test.

Prior to June 4th blood pressure readings, on no medication other than sedatives, varied systolic between 170 and 300, diastolic between 100 and 150.

On June 4th hexamethonium chloride 0.04 cc. (100 mg. per cc.) was administered intravenously. The patient promptly went into shock, blood pressure 70/50, from which there was gradual recovery with the use of norepinephrine.

Thereafter hexamethonium chloride was given subcutaneously in combination with oral Rauwolfia and blood pressure ranged between 120/65 and 280/140, the general condition of the patient seeming to be much better when the blood pressure was in the lower ranges. By July 10th, however, the patient was becoming refractory to these drugs and they were discontinued.

On July 15th, right nephrectomy was performed by Dr. H. C. Brickman. The kidney was small and there was no palpable pulse in the renal artery. Approximately 1½ inches from the hilum of the kidney, there was seen an anomalous vessel extending from the main renal artery to the upper pole of the kidney. The postoperative course was uncomplicated. On the first postoperative day, blood pressure readings varied between 140/55 and 170/90, rose to a maximum on the fourth day of 200/120 and thereafter fell gradually so that at discharge on the 10th postoperative day the lowest reading was 140/75 and the highest 160/90.

The patient was seen by Dr. Watson at her home on October 12, 1953. She had resumed full activity and was feeling perfectly well with none of her previous symptoms. She was most enthusiastic about her improvement. The eye grounds had improved considerably. Disc margins were now clear and hemorrhages and exudates were disappearing. Resting blood pressure was 140/70, and general examination was normal. A voided specimen of urine had a specific gravity of 1.012 and contained a trace of albumen with 10–12 WBC in the sediment. However, when seen the following week at the Woman's Hospital in a nervous state the blood pressure was found to be 190/105. She was still entirely asymptomatic.

*Pathological findings:* The kidney* was small, weighing 110 grams and measuring 9.5 by 5.5 by 3.5 cm. The capsule stripped with ease, leaving a finely granular surface with an occasional small pitted scar. A few tiny cysts were present. On cut surface, the cortex was slightly reduced in width but showed relatively normal striations. The pyramids, calyces and pelves were normal in size but the mucosal surfaces were granular. Microscopically, there was a definite round cell infiltration of several calyces and of the pelvic wall. Intrarenal arteriosclerosis was very prominent both of arcuate and interlobular arteries. Several arteries were occluded by fibrous masses in which clefts were present typical of cholesterol. These lesions were considered characteristic of healed atheromatous emboli (Fig. 12). Hyaline arteriolosclerosis was rare. Most glomeruli were normal. Marked tubular atrophy had occurred in large wedge-shaped cortical areas with preservation of glomeruli in such areas (Figs. 12 and 13). Prominent round cell infiltration of the parenchyma was present but no periglomerular scarring was seen. A very rare focus of tubular dilatation with casts was noted.

*Summary:* A 53-year-old woman had been told for several years that her blood pressure was somewhat elevated. She was admitted to the hospital with severe hypertensive encephalopathy, the symptoms of which included convulsions and mental confusion. The first intravenous pyelogram disclosed no opaque medium in the right kidney and no urine was obtained from this side. A later study showed a trace of opaque medium and very little urine. The right kidney appeared to be very small. Right nephrectomy was carried out. Blood pressure fell gradually and she improved rapidly. Three months postoperatively she had resumed full activity and was symptom free. Her eyegrounds were clearing and resting blood pressure was 140/70. However, when nervous or excited the patient's blood pressure was noted to rise to 190/105.

## DISCUSSION

Almost 45 years ago, Janeway (5) showed that, when constricting ligatures were placed about the renal arteries of dogs, the postoperative blood pressure persisted at significantly elevated levels for more than a month. Since that time much evidence has accumulated, including Goldblatt's classical experiments

* This specimen was studied through the courtesy of Dr. Beissinger, Women's Hospital, Baltimore, Maryland.

(1), which indicates an important cause and effect relationship between the vascular supply of the kidneys and the blood pressure. For the most part these many studies have dealt with problems of the etiology and pathogenesis of hypertension, concerning which there is still a great variance of opinion. Pathological study of autopsy material has yielded the additional evidence that persons who have had sustained hypertension, without primary renal disease or adrenal medullary tumors, usually disclose morphological changes in the renal vascular bed compatible with a vascular insufficiency of the kidneys. While such vascular lesions are usually found to be bilateral, an occasional case of unilateral disease has been seen (6a, b, c, d, e, f, g, h, i). These latter autopsy findings, however, have not provided the essential evidence of the cause-effect relationship of such unilateral renal lesions to clinical hypertension. Removal of the kidney from animals with an *experimental* vascular constriction has proven this point by curing the hypertension. A few reports have appeared in the literature where a unilateral renal vascular lesion occurred in man, and the patient's hypertension was alleviated or eliminated by nephrectomy. The reports followed the initial observations by Butler (7), who first called attention to the effect of nephrectomy upon hypertension in unilateral pyelonephritis.

Perhaps the first reported case of pure unilateral vascular insufficiency with hypertension was that of a 6-year-old boy with a pelvic kidney (8). The removal of the kidney resulted in a permanent and now 15 year cure of the hypertension. While the vascular obstruction was believed to result from a peculiar anomalous mass of smooth muscle in the artery, re-examination of the original section now shows clearly that this "tumor" was an artefact of sectioning the vessel. No renal disease was present in the kidney. This case must be left as one of probable vascular insufficiency, perhaps dependent upon the aberrant location of the kidney. Howard, Forbes and Lipscomb (9) reported the cure of hypertension in a 5-year-old child by the removal of a kidney with a renal arterial aneurysm. Perry (10) reported two patients with malignant hypertension, each of whom was cured by removal of a kidney containing infarcts and areas of tubular atrophy. Shea, Schwartz and Kobilak's patient (11) was a 33-year-old man with a thrombotic stenosis of a renal artery, cured of hypertension by nephrectomy, and Cornwell (12) described a 35-year-old woman relieved of hypertension by the removal of an infarcted and atrophied kidney. Malisoff and Macht (13) reported the case of a 34-year-old woman in whom the blood pressure returned to normal following the removal of a kidney, the main artery of which was occluded by a thrombo-angiitic process. Perera and Hoelig (14) reviewed the literature and mentioned two additional cures of their own which had renal emboli. Thompson and Smithwick (15) add two more cases but nephrectomy in both instances was accompanied by thoraco-lumbar sympathectomies.

There seems little doubt that the hypertension in the cases reported in the literature, as well as in those of this report, was caused by the kidney which was removed. This is strong evidence that there is at least one variety of hypertension which is a result of overproduction of some substance by a diseased kidney rather than a result of an impaired excretion of a substance produced elsewhere. It is also clear that the hypertension resulting from such damaged kidneys is indistinguishable at the bedside from severe "essential" hypertension.

The pathological alterations uniformly found in our series of patients was evidence of reduced arterial blood supply to sizeable areas of the kidney or in some cases to all of the kidney. The cases may be roughly subdivided into three groups:

*Group A:* In two instances the main artery was believed at operation to be small and to pulsate less than does a normal renal artery. These were the cases in which no opaque medium appeared during intravenous pyelography and no urine was excreted by the affected kidney (Cases 3 and 6). In one of these (Case 3) there was generalized uniform atrophy of renal tubular parenchyma (Figs. 5 and 6); this is indeed a beautiful example of Selye's so-called "endocrine" kidney (16). In Case 6 there was a widespread and severe but focal tubular atrophy (Figs. 11 and 12). It is believed that, had arteriography been carried out, a gross defect in renal arterial flow would have been demonstrated in both these cases. It is unfortunate that the operators were unable for technical reasons to follow the renal arteries to the aorta in order to determine the exact site and nature of the original lesion.

*Group B:* In the two kidneys with wedge-shaped areas of infarction (Cases 1 and 2), zones of uniformly atrophied renal parenchyma were found around the necrotic areas. In Case 2 the infarct was very small, and an almost uniform tubular atrophy of two-thirds of the kidney (Figs. 1–4) indicated that vascular insufficiency had been present. It is believed that these atrophic zones were due to reduced blood supply to these specific areas and that hypertension was a consequence. Renal infarcts are commonly found at postmortem examination. Most of these infarcts have a relatively sharp line of demarcation between the necrotic and normal tissue, suggesting that the ischemia is usually limited to the zone of necrotic and completely non-functioning cells. This fact probably accounts for the rarity with which renal infarcts lead to persisting hypertension since remaining ischemic *but viable* renal parenchyma is probably essential for the excessive production of the substance causing hypertension. Persisting hypertension following renal infarction has been reported, (4, 10, 12, 14, 17a, b, c, d, e). There are also cases on record in which the hypertension was transient (4, 17a, 18). The return to normotension in such cases might be explained by subsidence of edema, by the improvement of blood supply with the de-

velopment of collateral circulation, or by the complete necrosis of the adjacent ischemic tissue.

*Group C:* In the remaining two patients of the present series (Cases 4 and 5), the microscopic appearance of the removed kidney was remarkably normal. In Case 4 the renal tubules appeared entirely normal, even when stained by a variety of techniques. Enzyme stains were not done. The juxtaglomerular bodies, however, were exceptionally prominent (Fig. 8). In the other (Case 5) there were scattered areas of very slight parenchymal atrophy. These two kidneys appeared perfectly normal by intravenous pyelography, yet in both instances abdominal aortography demonstrated defects in the renal arteries. In Case 4 the arteriogram demonstrated narrowing so close to the aorta and hidden by the vena cava, that the operator felt it unwise to explore the site. In Case 5 at operation a small ganglioneuroma (Fig. 10) lay upon the renal artery in such a way that it probably accounted for the failure of the renal artery to be visualized in the aortogram. It is postulated that in these cases the reduction in renal arterial flow was so slight that morphologic abnormality of the renal tubular parenchyma was not appreciable, yet functional changes were present which resulted in hypertension.

It will be remembered that morphological studies of the kidneys of the Goldblatt dog with persistent hypertension also usually fail to show appreciable tissue changes. Tubular atrophy, so prominent in our other cases, is only very rarely described in the dog with sufficient renal arterial constriction to cause severe hypertension.

The tissue changes which have been described in our cases are characteristic of renal ischemia. When the arterial blood flow to a kidney is severely reduced, either to a large area or to a small wedge-shaped portion supplied by one interlobular artery, convoluted tubules atrophy while glomeruli remain intact for much longer periods. It is believed that this is the consequence of the vascular needs of the highly complex metabolism of the tubular cell in contrast to those of the simple filtering structure which is the glomerulus. Furthermore, it would be impossible to discern atrophy in cells which exist normally as greatly elongated flat structures. Usually mild round cell infiltration accompanies the tubular atrophy. Tubular dilatation is not a component of simple atrophy and glomeruli show no cellular proliferation. Except in Case 6 there was no pelvic or calyceal inflammation or scarring, periglomerular scarring or other evidences of pyelonephritis. The prominence of the juxtaglomerular apparatus in Case 4 is of interest. Enlargement of this structure in the kidneys of experimental hypertension has been noted, whether that hypertension was produced by arterial constriction (19) or by cellophane encapsulation (20); and an occasional prominent juxtaglomerular body was seen in other cases in our series. But in Case 4, the apparent hypertrophy of this structure was the only ab-

normality noted. The juxtaglomerular body has been considered as a possible source of renin (19, 20, 21), but the importance of this structure in the pathogenesis of hypertension remains to be clarified.

Our patients have thus exhibited evidence of a reduction of arterial blood supply to a kidney; in some it was so slight that anatomical defects were not significant; in others there were local areas of tubular atrophy, and in the remainder there was general atrophy of the renal tubular parenchyma—all patients being relieved from their *severe* hypertensive states by nephrectomy although some of the patients continue to manifest some degree of hypertension, especially under stress. The period since nephrectomy in three of these cases has been of insufficient duration to meet the rigid criteria for the claim of permanent cure of hypertension. Yet the clinical and pathological observations, together with the dramatic improvement following nephrectomy, warrant the belief that in all cases the removed kidney was responsible for the severity of the hypertension.

In this series the duration of the vascular defect prior to the onset of hypertension cannot be stated precisely. In two patients it seems reasonable to suppose that the episodes of abdominal pain which resulted in removal of normal appendices were really due to the vascular insults which caused renal infarcts. Thus in these two cases the interval before hypertension became manifest was probably a matter of a few weeks. In this connection it is of interest to recall the occasional abrupt hypertension which follows certain forms of acute renal trauma. One such instance was seen by one of the authors in consultation with Dr. Richard T. Shackelford. A young man, previously normotensive, was kicked by a horse and entered the Union Memorial Hospital in severe shock from internal bleeding. After transfusion in preparation for operation, hypertension (systolic 300 mm. Hg.) developed. A ruptured kidney was removed, and within 24 hours the blood pressure had returned to normal. In another patient recently seen by Dr. Shackelford (22), a bullet wound of the abdomen was followed within a few hours by very severe hypertension. The parallelism to the previous case was recalled, and Dr. Shackelford explored with the prediction that the kidney would be involved in the bullet's damage; this concept proved to be correct. The blood pressure returned to normal within 24 hours after nephrectomy.*

In the presently reported series the response of the blood pressure to nephrectomy was usually quite prompt. In Case 5 there was no appreciable fall until the ninth day after which the pressure gradually receded to normal on the 14th postoperative day. Patient 4 was normotensive within 24 hours after operation and remained so. In Cases 1, 2, 3 and 6 there was an immediate postoperative fall followed by a rise (but not to pre-existing levels) for several days and then

* These cases will be reported in detail by Dr. Shackelford.

a slow steady decline. Within 14 days the blood pressure in Cases 2, 3 and 6 had fallen to their previously known levels. In Case 1 the blood pressure was 140/100 when discharged from hospital on the 25th postoperative day. Thereafter, daily blood pressures were not taken, but the family physician recorded it as 140/90 two months later. It should be noted that four patients in this series now manifest a labile blood pressure and are so-called "hyper-reactors", although each of them under conditions of repose have repeatedly been found normotensive. One of these patients (Case 3) had shown documented lability of blood pressure for many years prior to the onset of his severe sustained hypertension, and his blood pressure measurements are now exactly similar to those of 16 years ago. There is no evidence that the other three now "labile" individuals had previously exhibited variable blood pressures.

### DIAGNOSIS OF PATIENTS WITH UNILATERAL RENAL DISEASE CAUSING HYPERTENSION AND INDICATIONS FOR SURGERY

It is clear from past experience that unilateral renal disease may exist in persons having hypertension and *not* be the sole causative factor in the hypertension. There have been many instances in which anatomically and functionally abnormal kidneys have been removed with no alteration whatever in the course of the disease. This low percentage of "cures" resulting from unilateral nephrectomy has been emphasized by Perera (23). In Perera's series good results were achieved most frequently in those patients whose hypertension was of recent origin and whose course was rapidly progressive to the so-called "malignant phase". In all the cases of the present report, the severe hypertension was also of recent origin (although two of the patients had had mild hypertension for several years), and in all six the course was rapidly progressive. However, it seems premature to state that hypertension due to unilateral renal vascular disease must *necessarily* follow such a pattern.

The history of an unexplained attack of abdominal pain within the months immediately preceding the discovery of hypertension warrants the suspicion of a renal vascular insult. In two of our patients (Cases 1 and 2) the abdominal pain undoubtedly coincided with the vascular accident which resulted in the necrosis and surrounding area of renal parenchymal atrophy. The cause of the primary arterial lesions could not be determined in either case. When one meets a patient with acute hypertension, in whom a history of recent abdominal or flank pain is elicited, where there has been a recent trauma to the renal area or a surgical procedure to the kidney, and particularly when there is a known source of arterial embolization, unilateral vascular lesion should be strongly suspected.

Once suspicion has been aroused, on what grounds may one implicate an abnormal kidney as the cause of the hypertension? *It seems clear from these cases that the usual studies carried out in investigating renal function*; i.e., the

capacity to concentrate urine, the excretion of phenolsulphonphthalein, intravenous and retrograde pyelography—*may prove to be within normal limits, and yet an abnormality of one kidney may be the cause of the hypertension.* This is in direct contradiction to previously oft expressed pessimistic statements, such as "only seriously affected or non-functioning kidneys should be removed" (15), and "the advisability of nephrectomy must rest upon conservative and recognized *surgical* indications, and not upon the hope of reducing blood pressure" (24).

Some definitive criteria must be found by which such cases can be recognized, else one of two results will ensue: either patients curable by nephrectomy will continue to be overlooked or wholesale nephrectomies will be performed with very low incidence of therapeutic success.

By disclosing vascular abnormalities in the renal arterial tree, abdominal aortography has proven its clinical usefulness in the two cases (#4 and #5) of this report in which the procedure was used. It would surely have revealed the lesion in Cases 3 and 6 and it is believed from a recent aortogram made in a case with proven renal infarct that the lesions in Cases 1 and 2 (the infarcts) would have been revealed. This is not to imply that abdominal aortography is indicated in every instance where one kidney is suspected of producing hypertension. Indeed, in our most recent case (#6), the procedure was not carried out, since it was felt that nephrectomy was clearly indicated on other grounds and aortography was an unnecessary added risk.*

If one is fortunate enough to have a flat film of the abdomen or an intravenous pyelogram prior to the development of hypertension, a helpful clue may be derived by detecting shrinkage in size of the offending kidney. Care must be observed in having films made with identical technique. Distortion due to technique can be checked by measuring the vertebral bodies to see that they are of identical width in the two sets of films. In Case 2 by comparative kidney measurement a shrinkage of 1.5 cm. was detected in the long axis of the offending kidney during a period of two months. In Case 4 there was a "probable" shrinkage of 1 cm. between films taken six months apart (the first film taken prior to the development of hypertension and the second film taken just prior to operation). However, no exploration would have been carried out on this evidence alone. The abdominal aortogram clearly disclosed a constriction in the renal artery.

Is there a functional defect which may be identified and so implicate a kidney as the cause of hypertension? It seems clear from our cases that a kidney may be functionally impaired to the point of complete inability to secrete urine or opaque urographic media, or it may function sufficiently well to give a normal

* A review and evaluation of abdominal aortography with a description of the method employed in these cases will be published by Dr. Gould.

intravenous pyelogram, and yet in both instances the kidney may be responsible for the hypertension. We were fortunate in obtaining simultaneous urine collections from both ureters in one case (Case 4) in which normal intravenous pyelograms were obtained. In this patient the offending kidney yielded substantially less urine than that of the opposite side and the sodium concentration of this urine was lower than that coming from the opposite ureter. In this connection White's experiments (25) on dogs with reduced renal blood flow to one kidney are of much interest. Though his animals did not develop hypertension, increasing reduction of arterial flow resulted in a progressive fall in water and sodium excretion from the experimental kidney *before* there was any significant reduction in diodrast or inulin clearance. It would appear from the experience with Case 4 that the implications of White's experimental observations should be further investigated in man, i.e., that in those cases suspected of hypertension from unilateral renal vascular disease and in whom intravenous pyelograms are normal, the urine collected simultaneously from both ureters should be examined for volume output and sodium concentration.

In addition to the danger of infecting a previously sterile urinary tract, the results of this procedure must be cautiously interpreted. Experienced urologists recognize that ureteral catheterization may of itself alter renal excretory function. Furthermore, leakage around the catheters may occur and this must be estimated by collection of bladder urine during the test. When such leakage is sufficient to interfere with volume measurements, determination of the sodium concentration of the ureteral urines may still yield valuable information. At the present writing it is believed that there must be at least a 50 per cent reduction in urine volume from one side as compared with that from the other to be considered significant.

In the cases of this series there has been no characteristic response to drugs whereby hypertension due to unilateral renal vascular disease could be identified. Likewise there was no characteristic change in blood pressure during general anesthesia at operation.

How long may one wait for spontaneous recovery if hypertension develops after a known renal vascular injury? The longest duration of hypertension following renal infarction in which spontaneous recovery occurred was 21 days in cases we have been able to find reported in the literature. Ben-Asher's (18) patient was a 43-year-old woman who had been followed since age 12 with rheumatic heart disease and fibrillation. Six days following what appeared to be a renal embolus, the patient developed hypertension (160/100 with a maximum of 180/106 on the 12th day), and the blood pressure remained elevated for 21 days, then returned to its normal level. Fishberg's (17a) patient, who also almost certainly had a renal embolus, developed elevation of the previous hypertension the following day and the blood pressure returned to its previous level in 10 days. Arnold, Goodwin and Colston (4) reported two cases in which

aberrant renal vessels were ligated for the treatment of obstructive hydronephrosis. In one, the previously normal blood pressure rose to hypertensive levels (170/100 on the first postoperative day with a peak of 200/110 on the seventh postoperative day) and returned to normal on the sixteenth day after operation. In another, there was a definite mild hypertensive trend in the highest readings recorded each day, although there were numerous normal readings as well. This moderate transient rise in blood pressure lasted for about three months. In view of the fact that contralateral renal arteriolosclerosis may develop as the result of hypertension *per se*, it would seem wise at the present writing to wait no more than six weeks for the pressure to fall before advocating nephrectomy.

How great a reduction of function may be present in the non-offending kidney and still have nephrectomy offer likelihood of cure of hypertension? Except for Case 6, no patient in this series had more than a trace of albumen, all were able to concentrate the urine to 1.017 or higher, total phenolsulphonphthalein excretion was not appreciably reduced in any, and blood non-protein nitrogen was within normal limits in all. After recovery from dehydration, the findings in Case 6 likewise fulfilled these criteria. The urinary sediment of the two patients (Cases 3 and 6), whose offending kidney secreted no urine, contained only some white-cells and a few casts. Thus in the cases of this series the functional capacity of the contralateral kidney was excellent.

Thompson and Smithwick (15) performed biopsies of the "good" kidneys in both their patients and reported "early benign nephrosclerosis" in one, and in the other "grade 4 or marked changes in the vessels". Both these patients apparently made complete recoveries following nephrectomy, and these authors stress "the reversibility of hypertension even in the presence of marked arteriolar disease". It would seem clear that the presence of significant vascular disease in the remaining kidney, even if such biopsies are representative of the entire kidney, is not a contraindication to nephrectomy. But these biopsies show only the smallest of renal arteries and insignificant numbers of arterioles. Accurate estimation of the success or failure of nephrectomy based upon such biopsies is clearly impossible. It is probable, however, that the failure of nephrectomy to alleviate hypertension has been most often dependent upon contralateral renal disease. The gradual, rather than abrupt, return of the blood pressure to normal in some of our patients as well as in some reported in the literature may be related to a gradual readjustment of circulation in the contralateral kidney.

The mechanism of sustained hypertension associated with pheochromocytomas has long been puzzling. The severe and abrupt paroxysms of hypertension produced by these tumors seem reasonably explained by massive discharges of norepinephrine or epinephrine. But many cases of pheochromocytoma exhibit sustained hypertension, indistinguishable at the bedside or by

ordinary tests from "essential" hypertension (26a, b, c, d). Some of these cases have shown prompt fall of blood pressure in response to intravenous injection of an epinephrine and nor-epinephrine competitor, but other cases also "cured" by removal of such tumors have not responded to benzodioxane in the doses employed (27a, b, c, d). Furthermore, some patients with pheochromocytomas and sustained hypertension (*not* necessarily those who gave positive benzodioxane tests before operation) exhibit an immediate fall in blood pressure as soon as the venous return from the tumor is cut off; whereas others (not necessarily those with negative benzodioxane tests before operation) respond to the tumor's removal with no immediate change in blood pressure—the pressure falling gradually over a period of 20 to 60 days. This gradual fall from hypertension to normotension is also the usual pattern after removal of adrenal cortical tumors that have produced Cushing's syndrome. The mode of recovery from the hypertension after removal of the offending agent is quite similar in all three of these conditions. One cannot help wondering if the hypertensive mechanism in these cases of pheochromocytoma and adrenal cortical tumors may not be similar to that of the cases in this report—namely, reduced renal arterial flow. Likewise the hypertension associated with pyelonephritis and glomerulonephritis can well be conceived to result from renal ischemia.

## SUMMARY

This report concerns six patients with severe hypertension, who were greatly improved by removal of a kidney.

In all patients there was unequivocal evidence of impaired blood flow to the kidney which was removed.

Two patients gave histories consistent with recent renal infarction, and both these patients had intravenous pyelograms which had been interpreted as normal.

Abdominal aortograms were made in two instances, and constriction or occlusion of the major renal artery was demonstrated in each. Intravenous pyelograms were read as normal in both of these patients.

In the two remaining cases no dye was demonstrable in the offending kidney nor was urine secreted by them, although retrograde pyelography demonstrated normal collecting systems.

In one patient urine flow and urinary sodium concentration from the offending kidney were sharply reduced as compared with those from the opposite side *despite normal intravenous pyelography*, and led to the performance of aortography.

Pathological changes seen in these kidneys include renal infarcts with surrounding tubular atrophy, diffuse tubular atrophy without infarction and moderate to very slight focal tubular atrophy. In one case no morphological evidence of vascular insufficiency was present, although in this patient im-

paired renal blood flow had been demonstrated by aortography. The extent of the tubular atrophy was comparable to the demonstrated renal excretory dysfunction in this series of patients.

These cases present further evidence that hypertension in man can be produced by unilateral renal ischemia and may be curable by nephrectomy.

## ADDENDUM

Since the writing of this report, we have had the opportunity to carry out differential renal function studies on two additional cases of hypertension resulting from unilateral renal vascular disease. These observations lend support to the suggestion in the paper that differential function may be a useful procedure in recognizing this type of hypertension.

In the first of these cases (J.H.H. #647838), seen through the courtesy of Dr. H. F. Klinefelter, Jr., the right kidney was supplied by a number of small anomalous arteries, no main vessel being present. Many of these arteries were occluded by cholesterol emboli and this resulted in widespread renal tubular atrophy. The volume of urine from this kidney in 30 minutes was 9 cc. compared with 22 cc. from the left. The sodium concentration of the urine from the right kidney was 99 mEq. per liter, that from the left was 117 mEq. per liter. These findings led to the performance of an abdominal aortogram which demonstrated the vascular defect. The patient was greatly improved when seen 2½ months after right nephrectomy. The second case (J.H.H. #641601), seen through the courtesy of Dr. Alfred Blalock, did not have a nephrectomy, but almost certainly had an embolus and infarct of the right kidney 14 days after the surgical ligation of a patent ductus arteriosus. Two other embolic phenomena were observed, a hemiplegia and an iliac occlusion, the latter surgically removed. She was first noted to have hypertension of 160/120, 17 days after the renal embolus (no blood pressure readings were recorded during the preceding two weeks). Later recordings were as high as 185/140. Bilateral ureteral catheterization was performed. Unfortunately, leakage around the catheters interfered with volume measurements. However, the sodium concentration of the urine from the involved side was 21.8 mEq. per liter, whereas that from the other side contained 31.0 mEq. per liter. An aortogram was not done. Because of the multiple previous surgical procedures operation on the kidney was postponed. Over the course of the next 10 weeks, blood pressure gradually fell to 126/96. One might conclude from this observation that readjustments in the kidney can occur gradually and it might be wise to wait more than six weeks after a known renal vascular insult has caused hypertension before advising nephrectomy.

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## EXPLANATIONS OF ILLUSTRATIONS

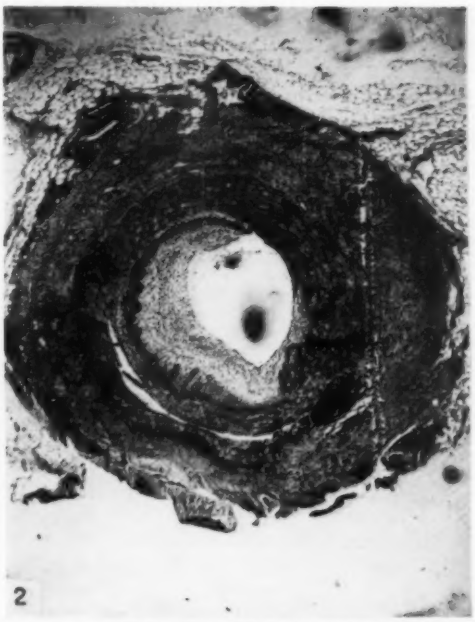
(Photographs by Joan Bailey

FIG. 1 (P. C., Case 2). The kidney showed an irregular line separating the atrophic from normal cortex (B). An aberrant artery supplied the upper pole (A).

FIG. 2 (P. C., Case 2). The main renal artery to the lower ⅔ of the kidney was greatly narrowed by fibrous intimal thickening. This could represent a healed mural thrombus. There is adventitial scarring.

FIG. 3 (P. C., Case 2). Atrophic renal tubules adjoining normal tubules which lie in the left center of the field.

FIG. 4 (P. C., Case 2). Atrophic tubules in the lower half, normal tubules above. Glomeruli all normal.



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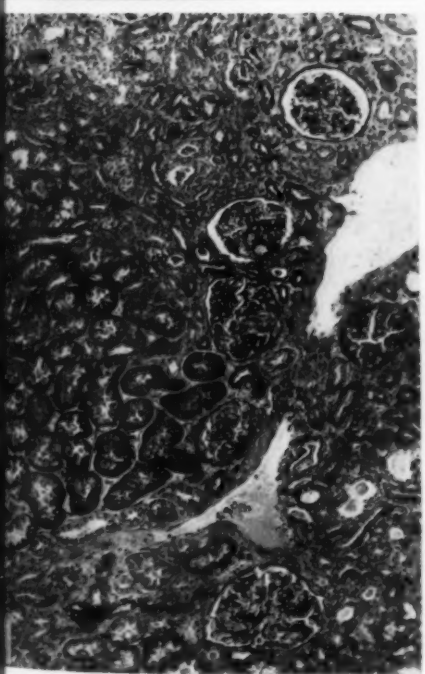

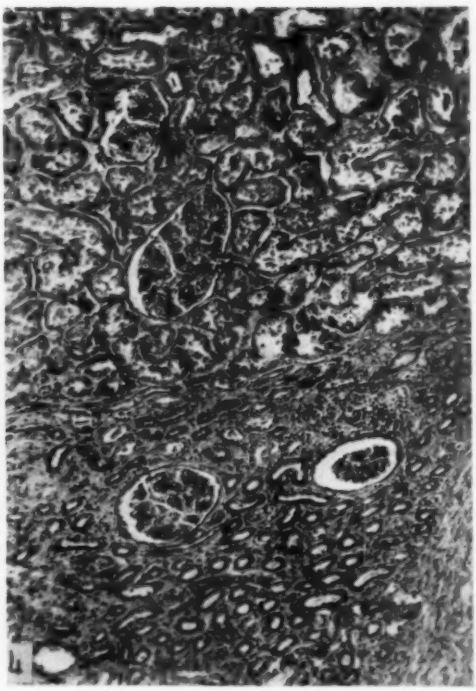

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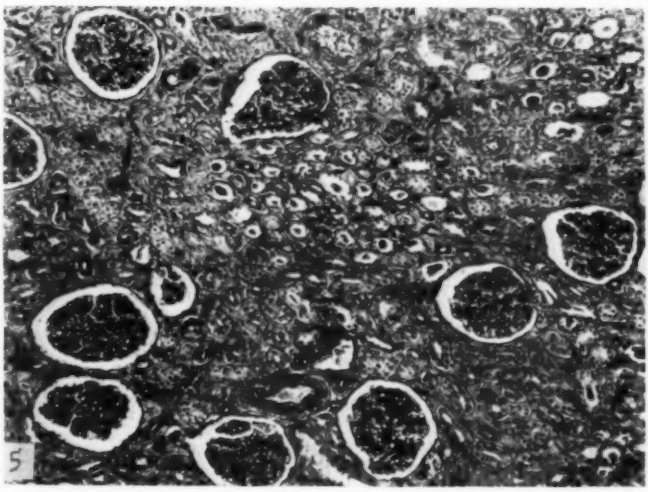
FIG. 5 (M. G. P., Case 3). Marked atrophy of tubules with resulting condensation of glomeruli.

FIG. 6 (M. G. P., Case 3). High power magnification of atrophied renal tubules. Note normal glomerulus and juxtaglomerular body.



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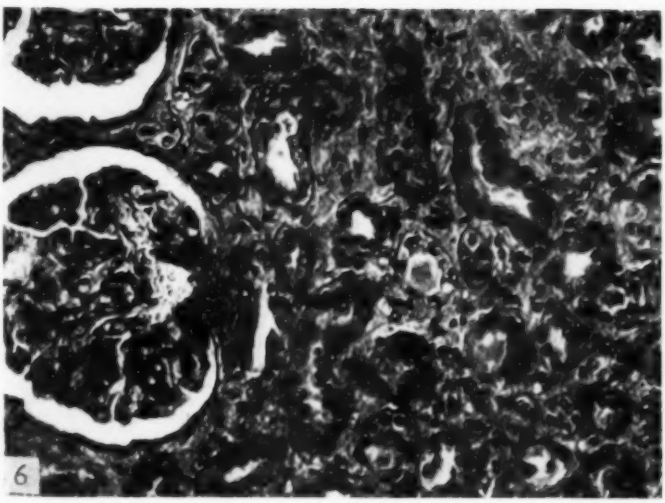

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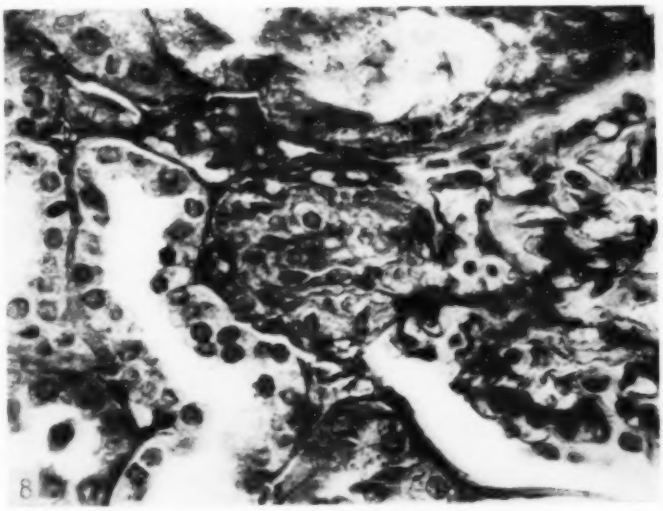
FIG. 7 (I. N., Case 4). Abdominal aortogram. The arrow points to the constriction of the right renal artery.

FIG. 8 (I. N., Case 4). Hyperplastic juxtaglomerular body with normal glomerulus and renal tubules.

FIG. 9 (J. D., Case 5). Portion of the well differentiated ganglioneuroma. Serial blocks did not show tissue suggestive of pheochromocytoma.



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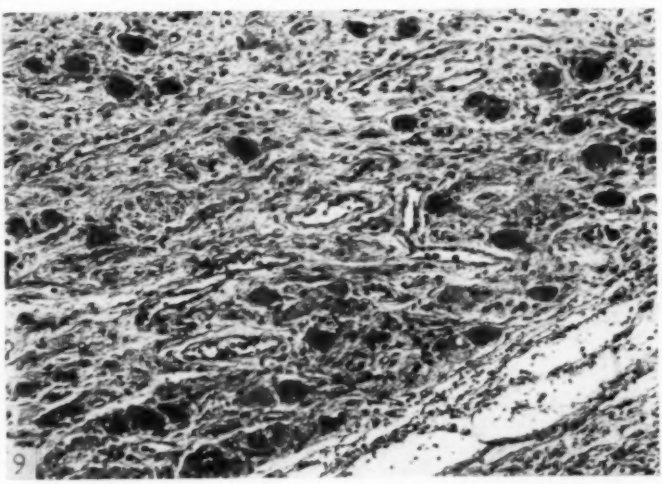

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FIG. 10 (J. D., Case 5). Retrograde abdominal aortogram. The left renal artery did not fill with opaque medium. The arrow points to the splenic artery.

FIG. 11 (J. D., Case 5). Retrograde abdominal aortogram with opaque medium outlining left kidney. Arrow points to the left ureteral artery through which renal vessels were thought to receive opaque material.

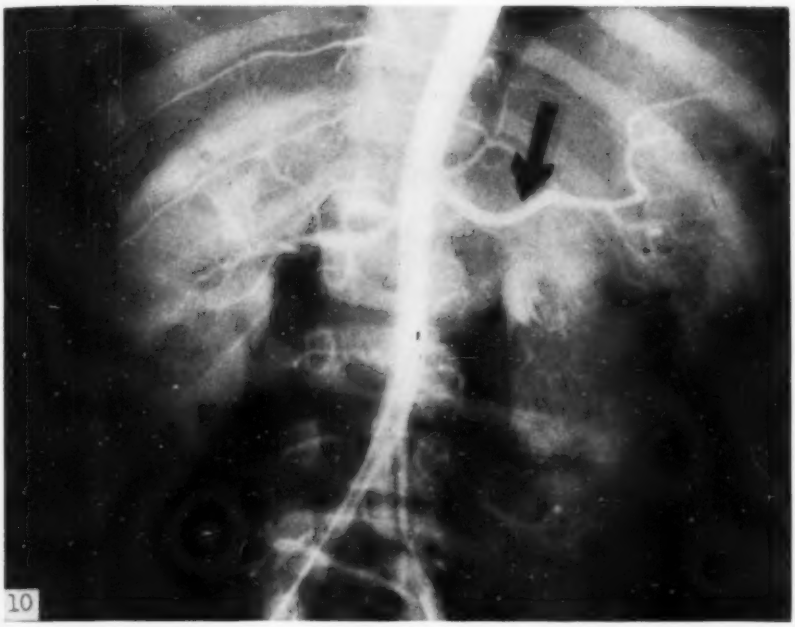

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FIG. 12 (E. G., Case 6). The renal tubules are markedly atrophic with preservation of glomeruli. Slight tubular dilatation is seen. A vessel shows fibrous intimal thickening with clefts typical of a healed embolus of an arteriosclerotic plaque.

FIG. 13 (E. G., Case 6). Marked tubular atrophy is present throughout the section.

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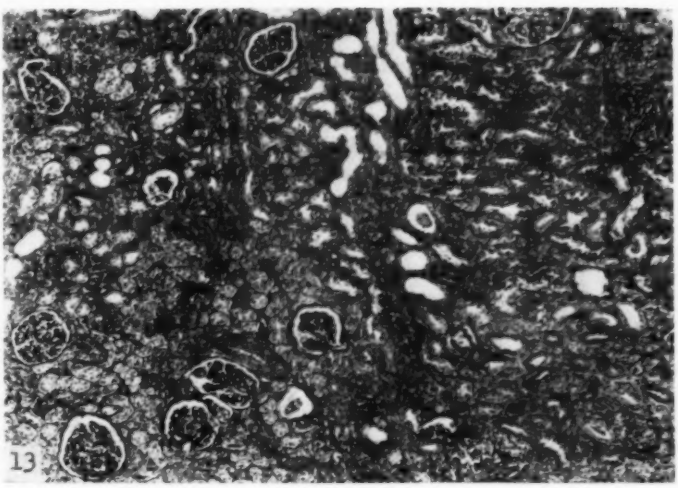

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# MASSIVE PULMONARY EMBOLIZATION BY CEREBRAL CORTICAL TISSUE

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Received for publication December 11, 1953

Pulmonary emboli formed of substances other than thrombus material have occasionally been found at autopsy. Among these unusual materials, fragments of bone marrow have been found as pulmonary emboli by Fisher (1); liver tissue emboli were found by Strauss (2); and Krakower (3) reported finding a small embolus of brain tissue in the lung of a 23 months infant. This infant developed hemiplegia following a fall; an exploratory craniotomy was performed, but she developed an irregular pulse and air hunger and died shortly thereafter. The autopsy showed a single small plug of brain tissue in a small pulmonary artery and numerous thrombotic emboli and infarcts.

The present case is unusual in that massive brain emboli were found in the lungs and, presumably, were the immediate cause of death.

## CASE REPORT

H. P.—42 year old white male (History No. 411644) was brought to the accident room of this hospital 8-8-51 at 2:30 A.M. by the police. He had been drinking heavily and had fallen down the stairs at his home 30 minutes before. On admission, he was stuporous, both pupils were dilated, and he was bleeding from the left ear. There was a large hematoma of the occipital scalp, and blood was seen in the pharynx. B.P. 120/84; P-80; R-18. At that time, no localizing signs were present. X-rays were made and showed a large diastatic fracture of the left lambdoid suture which extended down to the petrous ridge. At 4 A.M., B.P. 140/74, P-60. The left pupil was markedly dilated, the right constricted; neither reacted to light. There was frank papilledema with hemorrhages on the left; the right fundus could not be seen. There was a flaccid paralysis of the left arm. The patient did not respond to pin prick; knee jerks were equal; no other reflexes obtained. The patient was taken to the operating room at 5:40 A.M. Burr holes were made in the right and left temporal regions, at the vertex and left occipital region. The brain was under extreme pressure and mushy brain herniated spontaneously. There was considerable subdural blood in all the regions that were trephined but no localized hematoma was found. A calibrated ventricular needle (modified Frazier brain exploring canula) was inserted into each hemisphere but no blood or cerebro-spinal fluid was obtained. Lacerated brain tissue and subdural blood was aspirated, but the patient developed Cheyne-Stokes respiration at 6:20 A.M. As his condition was rapidly deteriorating on the table, the wounds were closed, but he died at 6:50 A.M., five minutes after arrival in the recovery room, and four hours and fifty minutes after his fall.

The clinical impression was: 1) Cerebral contusion, severe. 2) Acute subdural and subarachnoid hemorrhage, secondary to 1).

Autopsy 23172 was performed six hours after death by Dr. Edward Andrews. Only the positive findings are included in this summary.

*External Appearance:* The scalp was completely shaven. Fresh operative incisions were

present as follows: a left temporal region incision 6 cm. long; a right temporal incision 4 cm. long; a left parieto-occipital incision 3 cm. long; and a left frontal incision 4 cm. in length. There was subcutaneous swelling beneath the left parieto-occipital incision and bruises over the occiput. Bright red blood oozed from the left ear.

*Skull and Cranial Cavity:* There was a fracture of the skull starting in the rim of the foramen magnum and extending laterally for 6 cm. into the left posterior fossa. At this point, there was another fracture line, perpendicular to the first, extending 8 cm. posteriorly and anteriorly into the petrous bone. There was hemorrhage into the mastoid cells, inner and middle ears. Trephine holes were present in the skull beneath each of the four scalp incisions; and beneath each of the skull defects there was a shallow excavated laceration into the cortex of the brain, doubtless resulting from the marked tendency of the brain to herniate through the operative openings. There was no epidural hemorrhage except at the site of the four burr holes. There were scattered subdural hemorrhages, the largest 2 cm. in diameter; subarachnoid hemorrhage was present over the left frontal and temporal lobes, along the sagittal sinus and at the base of the brain. There was superficial laceration of the left temporal lobe, which in addition, was soft, mushy and blood stained. There was also superficial laceration of the left frontal pole and right anterior parasagittal region of the brain; and subpial petechiae were seen in the cortex and white matter of these areas. A small surgical perforation, measuring 1 cm. in diameter was noted in the left frontal paracentral region. This defect extended into the white matter. The basal ganglia and ventricles were normal. Petechiae were present in the cortex at the base of the left temporal lobe as far medially as the hippocampus and in the occipital lobe almost to the occipital pole. There were a few petechiae along the margins of the pons. No thrombi were found in the dural sinuses or in their branches.

*Lungs:* The lungs weighed 800 grams together and were air-containing throughout. The bronchi contained a small amount of aspirated vomitus. The pulmonary arteries of all sizes projected conspicuously above the cut surfaces and were seen to contain "white clot which is readily dislodged". (Fig. 1).

*Microscopic Examination:* Sections of the brain showed extensive cortical damage, especially on the left where there was widespread petechial and perivascular hemorrhage. The petechiae were confluent in the temporal and paracentral areas and in the tip of the frontal lobe. In these sections, the hemorrhage was associated with focal infarct-like necroses. Here, the nerve cells contained pyknotic nuclei and the tissue showed extreme edema. In the areas of cortical necrosis beneath the burr holes, there were small subpial defects with ragged margins (Fig. 2). There was considerable subarachnoid hemorrhage overlying the areas of lacerated cortex with extension to the arachnoid of adjacent normal brain. Pigment-laden macrophages were already present in the meninges in the areas of hemorrhage. Several small, hemorrhage-filled tubular cavities extended into the white matter and suggested damage resulting from needle punctures. The eyes showed subarachnoid and subdural hemorrhages in the optic nerve sheaths as well as small retinal and preretinal hemorrhages.

Sections of the lungs showed a mild chronic bronchitis consisting of slight interstitial lymphocyte and macrophage infiltration of the bronchial walls and muco-purulent exudate in their lumen. There was no pneumonia. The large intra-pulmonary arteries were conspicuous in every section of lung because of prominent plugging with embolic material (Fig. 3). This was clearly seen to be composed of cerebral cortical tissue with well-preserved nerve cells of entirely normal appearance, and well-preserved glial and vascular elements (Figs. 4 and 5). Many of the smaller pulmonary arterioles were plugged by similar emboli of cerebral material and occasionally a shallow bit of very fresh thrombus material adhered to the cerebral tissue (Fig. 6); a few small arterioles contained fresh thrombi; and others con-

tained blood or were empty. In all, nine sections of lung were made, and in each section there were numerous emboli of cerebral cortex.

*Anatomical Diagnosis:* History of acute alcoholism, fall and head injury. Fractures of the skull. Subdural, subarachnoid, cortical and pontine hemorrhages. Lacerations, cerebral cortex at sites of trephine holes and elsewhere. Multiple pulmonary emboli composed of cerebral cortical tissue. Small thrombi, pulmonary vessels. Chronic bronchitis.

## DISCUSSION

The occurrence of pulmonary emboli formed of cerebral substance is a rarity. I have been able to find only one other report of cerebral material found in pulmonary arteries (3). That infant suffered a head trauma for which exploratory craniotomy was performed. The autopsy showed the presence of massive thrombotic pulmonary embolism, and symptoms relating to this accident occurred after the craniotomy. The single minute cerebral tissue embolus found was too small to have produced any symptoms.

In the present case, emboli of cerebral cortical tissue filled the majority of the large intra-pulmonary branches of the pulmonary artery. This accident in combination with extensive brain damage, was probably responsible for death. Though dilatation of the right side of the heart would be expected, considering the widespread pulmonary embolism, this was not noted in the autopsy protocol. The exact cause of the embolization is impossible to determine. Only symptoms of increasing intracranial pressure were present before operation. It seems probable, therefore, that the alteration in respiration noted by the anesthetist thirty minutes before death marked the onset of embolization. Possibly this was associated with the release of cerebral pressure when cerebral cortex was seen to herniate externally. At this time, the lacerated cerebral tissue could also have been forced into traumatized dural sinuses. It is interesting, however, that no unusual hemorrhage occurred at any time during operation which might have indicated venous injury. Probably the extremely high cerebral pressure masked any such injury by plugging torn veins with the herniating cortex.

This appears to be an unusual if not unique accident. During the past twenty-five years at this hospital, there have been 277 complete autopsies on patients dying after intracranial operations. These cases have been reviewed and their lungs re-examined. Included in these 277 autopsies are 30 other instances of head injury with decompression operations similar to the case herein reported; there are 15 prefrontal lobotomies as well as 119 other cases of severely mutilating cranial operations. Thrombotic emboli were found in the lungs of 38 of these cases, but no other instance of embolization by cerebral material was uncovered. In the same period, there were 42 complete autopsies on cases of fractured skull without cranial surgery. The lungs from these cases were also re-examined; thrombotic emboli were present in 5 of these autopsies, but no embolic cerebral tissue was found in any of the lungs.

SUMMARY

This is a report of a case of traumatic skull fracture with intracranial hemorrhage treated surgically with multiple burr holes and decompression. An autopsy demonstrated the remarkable complication of widespread pulmonary emboli composed of well-preserved cerebral cortical tissue.

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(Photographs by Mrs. Joan Bailey)

FIG. 1. Hilar region of posterior half of upper lobe of left lung. Arrows indicate two longitudinally cut arteries plugged by emboli of whitish material. Similar emboli are seen in neighboring arteries cut transversely, while three vessels adjacent to the large hilar bronchus are empty. The emboli in very small vessels cannot be identified grossly.

FIG. 2. Area of typical cortical injury. Note ragged pia, loss of cerebral tissue and perivascular hemorrhages.

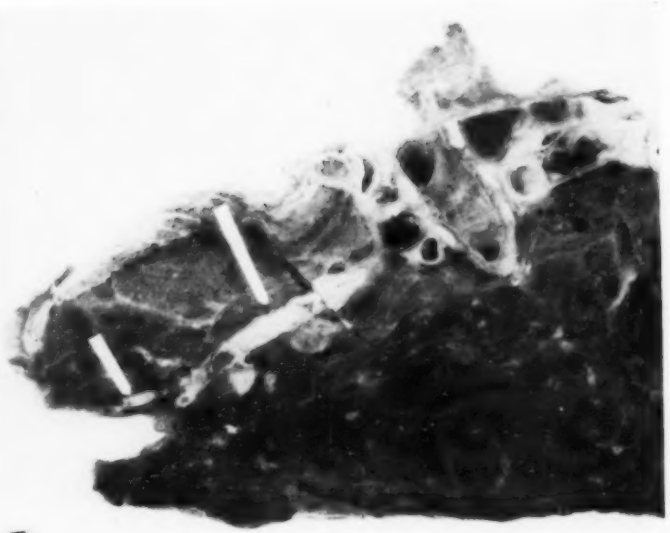

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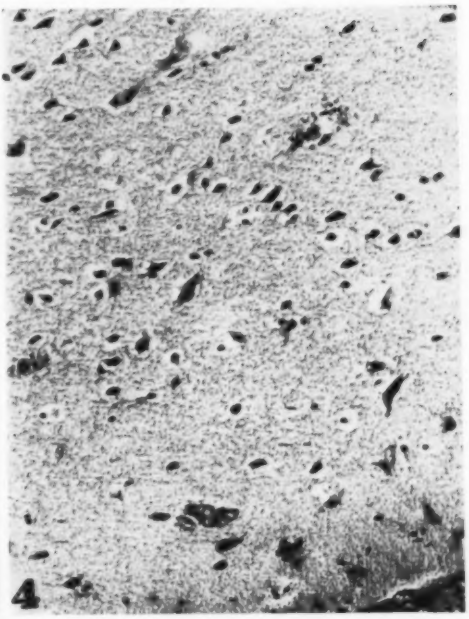
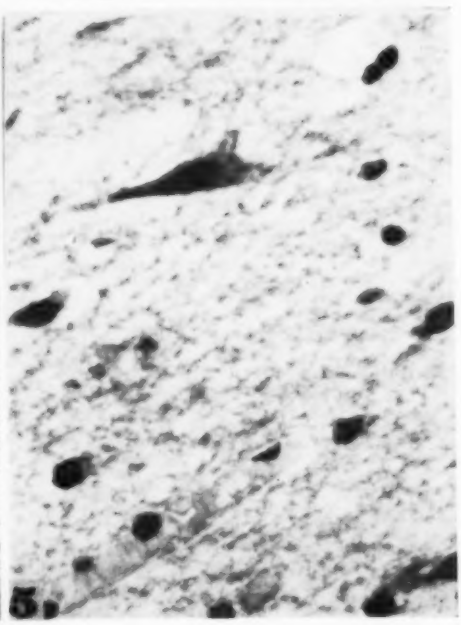
FIG. 3. Very low power magnification of lung (20×) showing large hilar pulmonary artery plugged with embolus of cerebral tissue. At upper right there is visible a segment of bronchial wall with two bronchial cartilages as well as exudate in the bronchial lumen.

FIG. 4. High power magnification (220×) of embolus in Figure 4, showing it to be composed of cerebral cortex with normal arrangement of neurons, glia and cerebral vessels. The margin of pulmonary artery wall is seen in the right lower corner.

FIG. 5. Very high power magnification (850×) to show the remarkable state of preservation of neurons in the embolus illustrated in Figures 3 and 4.

FIG. 6. Very low power magnification (20×) of lung to show distribution of emboli of cerebral tissue in small arteries. Thrombus material is also present in these three embolized arteries. A bronchus containing mucopurulent exudate occupies the center of this field.





# THE EFFECTS OF L-TRIIODOTHYRONINE AND L-THYROXINE ON THE METABOLISM OF TISSUES IN VITRO[1, 2]

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Received for publication December 15, 1953

In 1924 Rohrer (1) found that there was acceleration of the oxygen uptake of liver, kidney, or muscle isolated from mice treated with desiccated thyroid. Subsequently numerous investigators demonstrated an increased rate of oxygen consumption of various tissues removed from animals treated with desiccated thyroid or thyroxine; but it has never been shown conclusively that the addition of thyroxine directly to surviving *intact* tissues *in vitro* accelerates their oxygen consumption (2). Canzanelli and Rapport (3), Rossiter (4), and Williams and Whittenberger (5) reported that thyroglobulin augmented the rate of oxygen utilization of tissues *in vitro*, but Williams-Ashman (6) did not obtain such an effect. In previous experiments in this laboratory (7), neither *dl*-thyroxine nor two different preparations of highly purified thyroglobulin enhanced the rate of oxygen uptake *in vitro* of tissues isolated from normal rats. Since thyroxine exists in the serum combined with plasma proteins (8, 9) it was considered that it might be necessary for thyroxine to be bound to protein in order to be metabolically active. However, a specially prepared substance in which *dl*-thyroxine was coupled to gelatine also failed to increase directly *in vitro* the rate of oxygen consumption of tissues removed from normal rats (7).

Recently a hitherto unknown organic iodine compound, 3:5:3′-*l*-triiodothyronine, has been shown to be present in the plasma of animals (10) and man (11). It has been found that this compound is effective in increasing the metabolism of myxedematous individuals (12, 13, 14, 15) and is more potent than thyroxine in preventing goiter induced in rats by ingestion of thiouracil (16, 17). It appeared important therefore to determine the comparative

[1] Read in part before the Endocrine Society, thirty-fifth annual meeting, New York, N. Y., May 29, 1953, and in part before The Johns Hopkins Medical Society, December 14, 1953.

[2] Expenses of these studies were in part defrayed by a contract between The Johns Hopkins University and the Atomic Energy Commission, and in part by a grant from the Maryland Division of the American Cancer Society.

[3] This work was carried out during tenure of a Fellowship of the Damon Runyon Memorial Fund for Cancer Research, Inc., at The Johns Hopkins Hospital, 1951–53.

metabolic effects of *l*-triiodothyronine[4] and *l*-thyroxine[5] on tissues *in vitro*. Three types of experiments were performed. First, the effect on the rate of oxygen uptake of surviving intact tissues produced by the addition of *l*-triiodothyronine to the incubating medium was determined. Second, the rate of oxygen consumption of tissues isolated from hypothyroid rats which had been injected daily with *l*-triiodothyronine was compared with that of tissues of similar animals treated with equimolar amounts of *l*-thyroxine. Third, the metabolic actions of *l*-triiodothyronine and *l*-thyroxine on the oxidation of succinate by a rat heart homogenate-cytochrome *c* system were contrasted.

## METHODS AND MATERIALS

In the first series of experiments, tissues were obtained from normal male albino Sprague-Dawley rats. The animals weighed approximately 200 grams and were fed Purina dog checkers *ad libitum*. After fasting for 16 hours, each animal was sacrificed by a blow on the head, and the liver and diaphragm were excised and transferred immediately into an ice cold buffer solution. Blocks of liver tissue were sliced free hand so that the thickness of each slice did not exceed 0.5 mm., and the diaphragms were divided into halves and dissected free of large blood vessels and connective tissue. The individual liver slices or hemidiaphragms were blotted lightly on filter paper, weighed on a torsion balance and deposited in Warburg flasks containing 3.0 ml. buffer solution. Each tissue segment weighed approximately 50 mg. In the center well of each flask was placed 0.2 ml. 20 per cent KOH and a piece of filter paper. The vessels were attached to manometers, set in the water bath at 37.4°, gassed with oxygen for five minutes, and equilibrated for ten minutes. The manometers were shaken at a rate of 80 times per minute. Readings of oxygen uptake were taken every 30 minutes throughout eight hours of incubation.

The final concentrations of the constituents of the buffer solution were as follows: 0.131 *M* NaCl, 0.005 *M* KCl, 0.001 *M* $KH_2PO_4$, 0.013 *M* $Na_2HPO_4$, 0.002 *M* NaOH, and 0.005 *M* glucose. *L*-triiodothyronine was dissolved in 0.001 *N* NaOH and added to the buffer solution to give a final concentration of $3.0 \times 10^{-5} M$. An equal amount of 0.001 *N* NaOH was added to the control buffer solutions. The final pH of all solutions for incubation was 7.8. This pH was selected since *l*-triiodothyronine was more soluble at this point than at pH 7.4. At pH 7.8 calcium and magnesium salts precipitated out of solution and therefore they were omitted from the incubating medium. Six liver slices and two hemidiaphragms from each animal were incubated in pairs, i.e., one tissue segment was placed in a flask containing *l*-triiodothyronine, the other in a control flask without *l*-triiodothyronine.

In the second series of experiments male albino Sprague-Dawley rats weighing approximately 200 gm. each were thyroidectomized. Three weeks later each animal was injected intraperitoneally with 20 $\mu$c $I^{131}$; this should have provided adequate irradiation to destroy any remaining functional thyroid tissue (18). At least two months then elapsed before these animals were employed for experiments. Four weeks prior to the beginning of the test periods the animals were placed on a low iodine diet (19) so that a definite deficiency of circulating thyroid hormone would be induced, and they were maintained on this diet throughout the

[4] The 3,5,3′-*l*-triiodothyronine was obtained through the courtesy of Smith, Kline and French Laboratories from Glaxo Laboratories, Ltd., England, where it was synthesized.

[5] The *l*-thyroxine employed was in the form of sodium *l*-thyroxine pentahydrate which was kindly supplied by Dr. A. E. Heming of Smith, Kline and French Laboratories.

test periods. The animals were rendered hypothyroid since it has been shown that they would be much more responsive than normal animals to the administration of thyroxine (20).

*L*-triiodothyronine and *l*-thyroxine were dissolved in 0.02 *N* NaOH which was diluted with 0.155 *M* NaCl to pH 8.5. Fresh solutions were made every three days. The rats were divided into three groups and were injected subcutaneously daily for ten days with 0.10 ml. of the respective solutions. The first group received a control alkaline saline solution, the second *l*-thyroxine, and the third *l*-triiodothyronine. On the day following the final injections, and after a fast of 16 hours, the animals were sacrificed. Three liver slices and two hemidiaphragms from each animal were placed in Warburg flasks containing Krebs-Ringer phosphate solution at pH 7.4 with 0.011 *M* glucose and were incubated at 37° for one hour. Readings of oxygen uptake were recorded at 30 and 60 minutes.

In the third series of experiments the procedure followed was that originally devised by Gemmill (21) in which thyroxine accelerated the oxygen uptake of a rat heart homogenate-cytochrome *c*-succinate system. The components were added to the Warburg flasks as follows: 0.5 ml. $H_2O$, 1.6 ml. 0.5 *M* $Na_2HPO_4$ at pH 7.80, 0.3 ml. 0.001 *N* NaOH containing *l*-thyroxine or *l*-triiodothyronine or as a control solution, 0.2 ml. 0.0008 *M* cytochrome *c* in 0.08 *M* NaCl, and 0.4 ml. supernatant fluid from the rat heart homogenate; 0.2 ml. 0.31 *M* sodium succinate at pH 7.80 were placed in the side arms. The final volume was 3.2 ml. The homogenate was prepared by grinding 480 mg. heart muscle from a normal rat in 7.0 ml. ice cold 0.1 *M* $Na_2HPO_4$ at pH 7.80 in a glass homogenizer; the material was then centrifuged for five minutes and the supernatant fluid was used. The final concentration of *l*-thyroxine or *l*-triiodothyronine in the flasks was $3.1 \times 10^{-5} M$. The flasks, attached to manometers, were placed in the water bath at 37°. They were then gassed with oxygen for five minutes and equilibrated for ten minutes, after which the sodium succinate was tipped in from the side arms. Readings of oxygen uptake were taken every 15 minutes thereafter for three hours.

## RESULTS

*The effect of* l-*triiodothyronine on the oxygen consumption of tissues isolated from normal animals.* Five experiments were performed in each of which liver slices and hemidiaphragms from a normal rat were incubated with or without *l*-triiodothyronine in the incubating medium. The rate of oxygen consumption diminished with time; after eight hours of incubation tissue viability decreased to such an extent that values obtained beyond the last point had little meaning. It is observed (Fig. 1) that the presence of *l*-triiodothyronine in the incubating medium had no significant effect on the rate of oxygen utilization of the liver slices. Similar results were obtained when hemidiaphragms were incubated with or without *l*-triiodothyronine (Fig. 2). Cultures taken from all flasks at the conclusion of the incubations revealed no appreciable contamination with bacteria. Under the present experimental conditions, therefore, the addition of *l*-triiodothyronine directly to the incubating medium failed to enhance the rate of oxygen consumption of normal rat tissues suspended in the medium.

*The effect of daily administration of* l-*triiodothyronine or* l-*thyroxine to hypothyroid rats on the metabolism of their isolated tissues* (*Table I*). In order to obtain a distinct elevation in oxygen consumption of tissues isolated from ani-

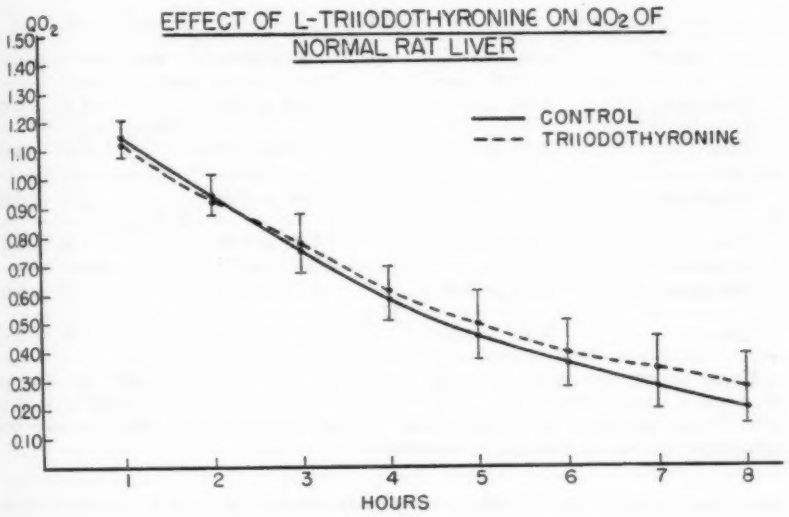


FIG. 1

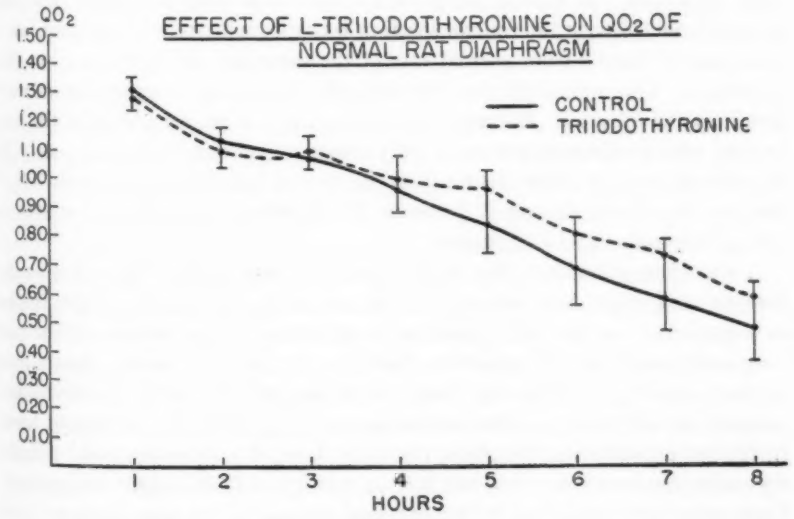


FIG. 2

FIGS. 1 and 2. Mean values from five experiments. Six liver slices and two hemidiaphragms incubated in pairs in each experiment. $QO_2$—cu. mm. oxygen uptake per mg. tissue (wet weight) per hour. Vertical bars—standard deviations of each mean. Initial pH 7.8. Final pH 7.4. See text for composition of incubating medium.

TABLE I

| | TISSUE | SALINE CONTROLS | DOSE | *L*-THYROXINE | DOSE | *L*-TRIIODOTHYRONINE |
|---|---|---|---|---|---|---|
| 1. | Diaphragm | 0.86 ± 0.04 | 136 μg. | 1.24 ± 0.06 | 100 μg. | 1.35 ± 0.07 |
| | Liver | 0.93 ± 0.05 | | 1.44 ± 0.05 | | 1.51 ± 0.08 |
| 2. | Diaphragm | 0.90 ± 0.07 | 6 μg. | 1.00 ± 0.03 | 4.39 μg. | 1.09 ± 0.08 |
| | Liver | 1.12 ± 0.08 | | 1.18 ± 0.05 | | 1.30 ± 0.05 |
| 3. | Diaphragm | 0.82 ± 0.03 | 12 μg. | 1.05 ± 0.04 | 8.78 μg. | 1.23 ± 0.06 |
| | Liver | 0.82 ± 0.06 | | 1.09 ± 0.09 | | 1.17 ± 0.12 |

Figures are expressed as cu. mm. oxygen uptake per mg. tissue (wet weight) per hour, and are means of values obtained from tissues of animals of each group. Standard error of the mean. 1—nine animals. 2 and 3—six animals. Two hemidiaphragms and three liver slices from each animal. See text for technique of incubations.

mals treated with *l*-triiodothyronine or *l*-thyroxine, the daily equimolar doses of the two compounds used in the first experiment were 100 and 136 μg. per kg. of body weight respectively. Three groups of nine hypothyroid rats each were employed. The rate of oxygen consumption of tissues isolated from the animals injected with the control solution was approximately 25 per cent lower than that of tissues from normal rats of the same age, as determined in this laboratory. This indicated that the animals used in these experiments were definitely hypothyroid. The rate of oxygen uptake of the tissues from the rats treated with *l*-triiodothyronine or *l*-thyroxine was elevated approximately 50 per cent above that of the tissues from the control hypothyroid animals. There was no significant difference between the metabolic stimulatory effects of *l*-triiodothyronine and *l*-thyroxine.

It was then considered that both *l*-thyroxine and *l*-triiodothyronine in the dosages used might have stimulated the rate of oxygen uptake of the tissues to a maximum so that any quantitative difference in the actions of the two compounds would not be apparent. Barker *et al.* (20) have shown that a dose of 12 μg. of *dl*-thyroxine per kg. body weight administered daily to a thyroidectomized rat will maintain the metabolism of the animal at a euthyroid level. In further experiments, therefore, the daily doses of *l*-thyroxine and *l*-triiodothyronine employed were 6.0[6] and 4.39 μg. per kg. of body weight respectively. There were three groups of six hypothyroid rats each. The rate of oxygen consumption of the tissues from the animals injected with *l*-triiodothyronine was not significantly different from that of the tissues from the animals treated with *l*-thyroxine, but neither drug effected more than a slight increase in the rate of oxygen utilization over that of the tissues from the control group.

[6] It was assumed that the *d*-thyroxine in *dl*-thyroxine is inactive.

In still further experiments of this type the daily doses of *l*-thyroxine and *l*-triiodothyronine used were 12.0 and 8.78 μg. per kg. of body weight respectively. Three groups of six animals each were utilized. Again there was no significant difference in the rate of oxygen uptake of tissues from the rats injected with *l*-thyroxine as compared to that of tissues from the animals given *l*-triiodothyronine. The rates of oxygen consumption of tissues from the animals of both groups were significantly elevated above those of tissues from animals of the control group. Although the differences between the effects of *l*-triiodothyronine and *l*-thyroxine were not significant at each dose level, the mean oxygen utilization was always greater following the administration of the former agent. Analysis of the data indicated that variation in the dosages of the compounds did not affect the difference between them in respect to their stimulation of the oxygen uptakes of the isolated tissues. The data from the three experiments, regardless of the dose of *l*-triiodothyronine or *l*-thyroxine, were therefore pooled, and analysis of variance revealed that the rate of oxygen consumption of tissues from animals given *l*-triiodothyronine was significantly greater ($p < 0.01$) than that of tissues from animals treated with *l*-thyroxine.

*The effects of* l-*triiodothyronine and* l-*thyroxine on the oxygen utilization of a rat heart homogenate-cytochrome* c-*succinate system.* The oxygen uptake of the systems containing *l*-thyroxine or *l*-triiodothyronine was far greater than that of the control systems (Fig. 3). During the first 75 minutes of incubation *l*-triiodothyronine accelerated oxygen consumption to a significantly greater degree than did *l*-thyroxine. Between 90 and 120 minutes the total oxygen uptake produced by the two compounds was of similar magnitude. For the remaining 60 minutes of incubation the oxygen utilization by the systems containing *l*-thyroxine was significantly greater than that by the systems containing *l*-triiodothyronine. When the values of oxygen uptake were plotted for each 15 minute interval (Fig. 4), it was apparent that *l*-triiodothyronine exerted a greater effect than *l*-thyroxine only for the first 30 minutes, but the difference was sufficient so that the integrated oxygen consumption of the flasks containing *l*-thyroxine did not approach that of the flasks containing *l*-triiodothyronine until 90 minutes had elapsed. The rate of oxygen utilization in the presence of *l*-triiodothyronine returned to the rate of the control reaction after three hours of incubation, whereas the process was still progressing at a significantly higher rate in the presence of *l*-thyroxine. The results of these experiments indicated that *l*-triiodothyronine had a more intense but less prolonged action than *l*-thyroxine in activating the oxygen utilization of the rat heart homogenate-cytochrome *c*-succinate system.

## DISCUSSION

There appears to be no ready explanation for the enigma that thyroxine injected into animals produces an acceleration in oxygen utilization of their isolated tissues but fails to increase the rate of oxygen uptake when it is added

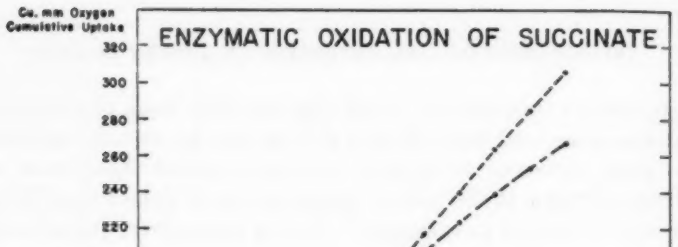


FIG. 3

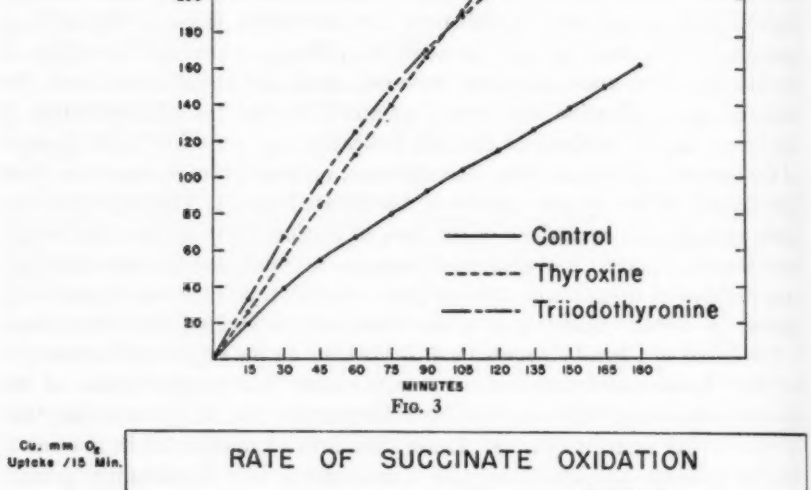


FIG. 4

FIGS. 3 and 4. Seven experiments. In each experiment 3 control flasks, 4 containing *l*-triiodothyronine and 4 containing *l*-thyroxine. Points are means of cu. mm. oxygen uptake per flask. Fig. 3—cumulative uptake. Fig. 4—uptake for each 15 minute period. Short bars—standard deviation of each mean. Initial pH 7.80. Final pH 7.76. See text for composition of incubating medium.

directly to intact tissues *in vitro*. A limiting factor to the direct action of thyroxine may be time. It has been found that at least ten hours must elapse following an injection of thyroxine into a rat before the oxygen consumption of its isolated tissues will be elevated above that of tissues of a rat treated with saline (7, 22). This suggests that time is required for thyroxine to be bound to or incorporated into the cell, to be changed into an active form, or to potentiate enzyme systems in the cell. It has been shown that a single injection of *l*-triiodothyronine elevates the metabolism of a myxedematous individual more quickly than does an equimolar dose of *l*-thyroxine (13, 14). It is conceivable, therefore, that triiodothyronine is the form of the thyroid hormone which is metabolically active in the tissue cell. The possibility arises that the time lag in the metabolic response of an organism to the administration of thyroxine may be due to an interval required by the peripheral tissues to convert thyroxine into triiodothyronine; such a conversion has been postulated by Gross and Pitt-Rivers (23). However, under the conditions of the first group of experiments reported herein, the addition of *l*-triiodothyronine directly to intact tissues *in vitro* did not stimulate the rate of oxygen utilization of those tissues even though the incubations were carried on for eight hours. Since readings of oxygen uptake were recorded every 30 minutes it is unlikely that *l*-triiodothyronine produced a rapid and transient increase in oxygen consumption which might not have been observed. The amount of *l*-triiodothyronine employed, 60 $\mu$g. per flask ($3.0 \times 10^{-5} M$), should have been ample to enhance the rate of oxygen consumption of approximately 50 mg. of tissue, since the administration of 500 $\mu$g. significantly elevated the metabolism of a myxedematous human being (13). The buffer systems in which the tissues were incubated were of relatively simple composition. One additional experiment has been performed in which rat diaphragms were incubated in a buffer solution which was diluted with an equal quantity of serum pooled from rats of the same group; addition of *l*-triiodothyronine to this medium caused no increase in the rate of oxygen uptake of the tissues. Apparently the presence of some factors as yet unknown must be required in order for *l*-triiodothyronine to be able to increase directly the rate of oxygen consumption of isolated tissues *in vitro*.

The question has arisen as to whether or not *l*-triiodothyronine is more active than *l*-thyroxine in potentiating tissue metabolism. Gross, Pitt-Rivers and Thibault (24), Deltour and Karamourtzounis (25), Heming and Holtkamp (26), and Tomich and Woollett (17) observed that *l*-triiodothyronine was four to five times as potent as *l*-thyroxine in elevating the basal metabolic rates of rats, when each compound was injected daily for several days. Maclagan *et al.* (27) administered single equimolar doses of *l*-thyroxine or *l*-triiodothyronine to mice. The basal metabolic rates of the mice given *l*-triiodothyronine rose significantly more rapidly than those of the mice treated with

*l*-thyroxine. However, the maximum elevation was reached between 40 and 60 hours after the compounds were injected and was of the same magnitude for both groups of animals. Thereafter, up to 100 hours there was no significant difference in the basal metabolic rates of both groups of animals. Gemmill (28) observed that *l*-triiodothyronine produced the same rise in the basal metabolism of normal rats on a weight basis as *l*-thyroxine when the animals were injected daily with either compound. The results of the present experiments, in which hypothyroid rats were treated for ten days with *l*-triiodothyronine or *l*-thyroxine at three different dose levels, indicated that *l*-triiodothyronine produced a slightly greater increase in the rate of oxygen consumption of the isolated tissues than did *l*-thyroxine. Since the solubilities of *l*-triiodothyronine and *l*-thyroxine are not identical, the rates of absorption and excretion of the compounds in the body may be quite different. A comparison of the metabolic activities of the two substances in this type of experiment may therefore not be accurate since the amount of each compound acting on the end organ is unknown. Furthermore both *l*-triiodothyronine and *l*-thyroxine may be converted in the tissues at different rates into another compound which then acts in the cell to accelerate oxygen utilization.

In the experiments in which *l*-triiodothyronine and *l*-thyroxine were incubated with rat heart homogenate, cytochrome *c*, and succinate, the incubations were allowed to proceed for three hours. The maximum rate of oxygen utilization by such a system occurred during the first 30 minutes as shown by the control curve in Figure 4. After 30 minutes the rate of oxygen uptake in the control system did not return to zero but proceeded at a constant level throughout the three hours of incubation. This provided sufficient justification to allow the reactions to progress for three hours and to compare the effects of *l*-triiodothyronine and *l*-thyroxine on the system throughout that period. No attempt was made to ascertain how the oxygen was being utilized or whether succinate was being consumed in the course of the reaction. The rate of oxygen utilization, although initially increased by *l*-triiodothyronine to a greater degree than by an equimolar quantity of *l*-thyroxine, returned to the control level more quickly in the presence of *l*-triiodothyronine than in that of *l*-thyroxine. If *l*-thyroxine itself were not metabolically active and should become active only when it was converted to *l*-triiodothyronine or if both compounds were changed into a third substance, the totals of oxygen utilization produced by the two compounds should have been identical, but this was not observed. Gemmill (29) likewise found that *l*-triiodothyronine accelerated oxygen uptake to a greater degree than did *l*-thyroxine in the rat heart homogenate-cytochrome *c*-succinate system during the first 30 minutes of incubation. He also reported (28) that the actions of *l*-triiodothyronine and *l*-thyroxine in this system were comparable on a molar basis when several different concentrations of the compounds were employed. It is interesting to note that the difference in oxygen uptakes of the homogenates produced by the addition of

*l*-triiodothyronine and *l*-thyroxine in the present experiments was very similar to the difference in the basal metabolic rates found in man after administration of *l*-triiodothyronine and *l*-thyroxine (13, 14).

The mechanism by which *l*-triiodothyronine and *l*-thyroxine augment the rate of oxygen utilization of the rat heart homogenate-cytochrome *c*-succinate system cannot be defined at present. Gemmill (21) did not observe acceleration of oxygen uptake on the addition of diiodothyronine or diiodotyrosine to the reaction mixture. In additional experiments in this laboratory, it was found that if *l*-triiodothyronine or *l*-thyroxine were added after one hour of incubation instead of at the beginning, no stimulation of oxygen consumption occurred. This observation suggests that some labile factor necessary to initiate the actions of the compounds is destroyed or is rendered otherwise unavailable. Further studies are being carried out in an effort to elucidate the mode of action of *l*-triiodothyronine and *l*-thyroxine in the stimulation of oxygen utilization by rat heart homogenate in the presence of cytochrome *c* and succinate.

## SUMMARY

1. The addition of *l*-triiodothyronine directly to buffer media containing liver slices or hemidiaphragms isolated from normal rats did not accelerate the rate of oxygen consumption of the tissues under the conditions of these experiments.

2. On daily administration to hypothyroid rats, *l*-triiodothyronine was slightly more potent than *l*-thyroxine in producing an elevated rate of oxygen utilization of liver slices and hemidiaphragms isolated from the animals.

3. *L*-triiodothyronine exerted a more intense but less prolonged action than *l*-thyroxine in activating the oxygen uptake by a rat heart homogenate-cytochrome *c*-succinate system.

## ACKNOWLEDGMENTS

The authors express their appreciation to Dr. John Eager Howard for his counsel throughout the period of these studies.

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# RÔLE OF HUMAN PLASMA PROTEIN FRACTIONS IV AND V IN 17-KETOSTEROID TRANSPORT

## Preliminary Report

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Received for publication November 10, 1953

When E. J. Cohn and associates began fractionation of human plasma during World War II, it was observed that the lipids of plasma were precipitated in combination with two types of protein (1). These proteins have been designated as: $\alpha$-lipoproteins (found in fractions IV or IV + V), and the $\beta$-lipoproteins (found in fraction III) (2). The possibility that the lipoproteins were related to the plasma transport of steroid hormones was suggested by Roberts and Szego, who found estriol to be combined specifically with the $\beta$-lipoproteins (3).

Owing to the recent development of a method for the determination of 17-ketosteroids in plasma (4, 5), measurements have been made of 17-ketosteroid concentration in several plasma protein fractions prepared by the techniques developed at the Department of Physical Chemistry at Harvard University.

### METHOD

One to 3 grams of the dry, protein fraction were added to 100 ml. of 10 per cent HCl and boiled for 12 minutes on a hot plate. The flask was cooled immediately, ether extracts were made and washed with 10 per cent NaOH solution (w/v) and then with water until neutral. The ether was taken to dryness and the residue redissolved in 70 per cent ethanol. This solution was washed with hexane, after which the ethanol fraction was extracted with chloroform and the latter chromatographed on magnesia-silica gel ("Florisil"). The eluate fraction known to contain 17-ketosteroids was taken off the column, the position of this fraction having been previously identified using crystalline dehydroepiandrosterone acetate and androsterone. A micro-Zimmermann reaction was done on the dry residue of this fraction, and the results expressed as micrograms of dehydroepiandrosterone acetate (5).

### RESULTS

Table I gives analytic data obtained from several human plasma fractions. Fraction IV-4 showed the highest concentration of 17-ketosteroids. No 17-ketosteroids could be detected in fractions I and II. Fraction VI was unavailable for analysis.

It is noteworthy that Roberts and Szego found estriol combined with fraction III (3), whereas the present study indicates that the plasma protein-bound 17-ketosteroids are principally associated with fractions IV-1, IV-4 and V. If the data are expressed per 100 ml. of whole plasma, the 17-ketosteroids bound by

TABLE I

*Values for 17-ketosteroid analyses on plasma protein fractions prepared by the methods of E. J. Cohn and associates. The data are expressed as micrograms per gm. dry powder*

| HUMAN PLASMA FRACTIONS | 17-KS μG./GM. | SOURCE OF PLASMA FRACTIONS |
|---|---|---|
| I | 0 | E. R. Squibb and Sons |
| II | 0 | E. R. Squibb and Sons |
| III | 1.4 | Armour Laboratories |
| IV-1 | 3.3 | Cutter Laboratories |
| IV-4 | 6.8 | Harvard University |
| V | 3.6 | Harvard University |

fraction V are quantitatively predominant, since approximately 50 per cent of the total protein in plasma exists as fraction V. There is also a considerable discrepancy between the total yield of 17-ketosteroids from the fractions noted in Table I and the values for 17-ketosteroids which have been obtained on whole, fresh plasma (5). The reason for this is not apparent, although it should be recorded that most of the plasma fractions available for analysis were at least four years old.

The data which have been obtained suggest that plasma protein fractions IV-1, IV-4 and V, and possibly III, are involved in the plasma transport of 17-ketosteroids. Since urinary 17-ketosteroid precursors are formed both in the adrenal cortices and testes, it is tempting to hypothesize that the plasma 17-ketosteroids are derived from these two tissue systems and in transport may be attached to different plasma protein fractions. It is quite possible that the $\alpha$-lipoproteins per se are implicated in 17-ketosteroid transport, however subfractionation of IV-4 will be necessary to elucidate this point.

## SUMMARY

Plasma protein fractions prepared by the technique of E. J. Cohn and associates have been analyzed for 17-ketosteroid content. Fractions IV-1, IV-4, and V showed the highest 17-ketosteroid concentrations of the fractions examined. The relationship of these findings to the transport of 17-ketosteroids in plasma is discussed, and the possibility that the protein-bound 17-ketosteroids of plasma are united with the $\alpha$-lipoproteins is raised.

## ACKNOWLEDGEMENTS

The author is indebted to Dr. Frank R. N. Gurd, University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University, who supplied several protein fractions. Thanks are due to The American National Red Cross, E. R. Squibb and Sons, Armour Laboratories and Cutter Laboratories for similar assistance.

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# PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

## Hurd Memorial Hall

## Monday, November 9, 1953

*Dr. W. W. Scott:* The meeting will please come to order. The first paper will be presented by Dr. Frederik B. Bang.

## CLINICAL AND PATHOLOGICAL ASPECTS OF HEMORRHAGIC FEVER IN KOREA

A general summary of present knowledge of the disease was presented. This included the recent review of the Russian literature on several types of hemorrhagic fever by Gajdusek. The description of the disease was accompanied by parts of a U. S. Army film on hemorrhagic fever which showed the clinical signs of the acute infection, the treatment of shock, and the gross pathological lesions. The clinical charts on several of the cases seen in Korea during the 1953 spring outbreak were presented and the difficulty of diagnosing mild cases was emphasized.

*Dr. Scott:* Thank you Dr. Bang. The next paper will be presented by Dr. George O. Gey.

### SOME APPROACHES TO THE PROBLEM OF THE ETIOLOGY OF HEMORRHAGIC FEVER

The etiologic agent of Far Eastern hemorrhagic fever has thus far not been identified or isolated. Direct transfers of blood and tissue materials from patients to animals have yielded only negative results. This report is concerned with attempts to isolate or demonstrate the existence of an agent by its effect on continuous cultures of human and rat normal and malignant cells.

At the request of the Commission on Hemorrhagic Fever of the Armed Forces Epidemiological Board, a series of tissue culture experiments were carried out in Japan and Korea by a team from Hopkins (Drs. Gey and Bang and Miss D. Minnegan) and including Miss M. Bozeman of the Department of Virus and Rickettsial Diseases of the Army Medical Service Graduate School. Dr. Joseph Smadel, director of this department at the Walter Reed Army Medical Center and chairman of the commission was responsible for getting this group into action on this problem, in the Spring of 1953. The project included the transport of tissue culture facilities to the Far East so as to permit the maintenance there of a variety of strains of adult human normal and malignant cells, of embryonic human cells, and a pair of rat normal and malignant cell strains. The work was carried out at the 406th Medical General Laboratory, A.F.F.E. in Tokyo with the help of Col. R. P. Mason, C. O., and his staff, and at the 48th M.A.S.H. in Korea with the help of Dr. Marshall Hertig, director of the Hemorrhagic Fever Laboratory, and of his staff.

Direct addition and prolonged exposure of fresh and frozen (−78°C) blood, serum, plasma buffy coat, and tissue materials from early cases of hemorrhagic fever (H.F.) to tumor strains HeLa (Epidermoid Carcinoma of Cervix) and AFi (Fibrosarcoma), both known to be susceptible to polio viruses and to strain D-1 Re (Chondromyxosarcoma), known to be susceptible to encephalitis virus (Eastern Equine), gave no evidence of cytopathogenic effects, even during long periods of exposure (approx. 1 month or more). The cultures were maintained in dilute human placental cord serum (30–50%) with the cells growing directly on the glass

wall of roller tubes before and during treatment with the suspected infectious materials. In some cases the exposure of cultures was practically a bedside procedure. Most of the cultures received no antibiotic treatment, either during routine maintenance, or during the experimental observation period.

Negative results were also obtained following prolonged exposure of such materials to cultures of adult normal human kidney epithelium and of fibroblasts of sternal marrow origin. A variety of human embryonic cultures (including organoids) from kidney, gut, heart, skin-muscle, iris and lens, lung, and adrenal continued active following exposure to frozen heparinized H. F. plasma (some were exposed to fresh H. F. plasma). These extended observations varied from 40 to 133 days with no cytopathogenic effects being noted. The normal rat fibroblasts, strain 14pf, and its malignant cell derivative, strain T-333, gave negative results also when managed in the same way. A few tissue cultures from skin petechiae were not remarkable.

Of the 13 separate inoculations made in this series, 12 cases were proved to be H. F.; one case was recorded as fever of unknown origin. An additional case (not in H. F. series) was thought to be a poliomyelitis-like infection (406 MGL, #53-1609); inoculation of material from pooled brain and cord produced a complete destruction of HeLa cultures within three days. Tissue culture passages in the HeLa cultures confirmed the initial destructive action in vitro. In the entire series, of 12 cases only one instance of a possible cytopathogenic effect might be inferred. In this one instance, 30% horse serum was used during a month's cultivation of strain HeLa, including a 10-day period of induced degeneration, followed by the addition of new cells. This one example of degeneration following the inoculation with fresh heparinized hemorrhagic fever plasma (H-708 Br.) needs to be confirmed. Other approaches to this problem by tissue culture and the use of organoids were outlined briefly.

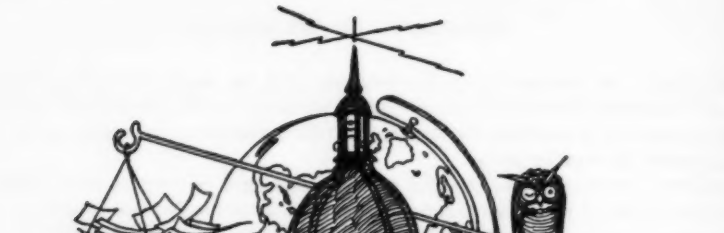
*Dr. Scott:* Thank you Dr. Gey. If we are to complete our program at a reasonable hour we shall have to dispense with discussion of these two most interesting papers. The next paper will be presented by Mr. Frank W. Law, Professor and Chairman of the department of Ophthalmology in the Guy's Hospital Medical School, London, and currently exchange visiting Professor of Ophthalmology in the Wilmer Institute.

## THE CHANGING FACE OF MEDICINE

Mr. Law gave an objective and critical review of the results of the implementation of the National Health Service Act in Great Britain. He reviewed the events which led up to the passing of the act, starting with the Insurance Act of 1911, and referred to the discussions which the bill provoked. He described the effect of the implementation of the act in its impact upon the patient's attitude towards medical care, upon the availability and quality of medical services, and upon the hospital services and the consultant. The review of medical practice, undertaken by means of personal inquiry by the British Medical Association and published just before the speaker left England, was considered in some detail.

The British government has recently set up a committee to inquire into the cost of the National Health Service, and the speaker was able to quote some opinions expressed in reply to this inquiry. He finally referred to the Public Health Service in Australia, and to a recent speech on the subject before the Annual Conference of the World Medical Associations, given by the Minister of Health of that country, Sir Earle Page; he also quoted from speeches made in the House of Lords during the debate preceding the second reading of the National Health Service Bill. He concluded by indicating how a consideration of his country's experience might be of value to the administrators in any other country who were contemplating the introduction of a National Health Service.

*Dr. Scott:* Thank you Mr. Law. The meeting is adjourned.



# BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

**Psychotic and Neurotic Illnesses in Twins.** Medical Research Council Special Report Series No. 278. By ELIOT SLATER. 385 pp., $4.75. Her Majesty's Stationery Office, London, England.

Dr. Slater is a prominent English psychiatrist. He was recently chosen to represent his specialty on the Royal Commission on Capital Punishment. He has published material chiefly on the relation of heredity to mental disorders and the use of physical methods of therapy in psychiatry. Some years ago, as a Rockefeller Fellow, he worked with Professor Rüdin in Munich.

The present research carried on under the aegis of the Medical Research Council, has extended over a period of nearly twenty years. Its basis is the idea propounded by Galton that a comparison of the incidence and character of a disease in both members of pairs of monozygotic and dizygotic twins will measure "in just scales the effects of nature and nurture."

The book begins with a thorough review of the previous psychiatric investigations making use of the twin method, with special attention to the important studies carried out at Columbia University by Franz Joseph Kallmann.

There is an extensive discussion of the biology of twinning with a very technical section on the use of finger prints to distinguish uniovular from binovular twins. Dr. Slater endorses the view that uniovular twinning is just as likely to be hereditary and hence occur in families as frequently as binovular twinning. He cites two studies that support his view but fails to mention the ten that do not. Dr. Slater acknowledges the existence of a possible "third variety (of twinning) partaking of the nature of both. Such a pair is supposed to arise from the fertilization of a single ovum and its polar body by two separate spermatozoa." Certain spermatoza carry with them "in the germ plasm a factor which causes the ovum on penetration to split off an exceptionally large polar body, so large as to be capable of fertilization and growth." This third type, known as oocytic twinning, would explain the established fact that the tendency to dissimilar twinning is carried by the male as well as the female line.

Dr. Slater's own material consists of 297 twin pairs, 66 uniovular, 225 binovular pairs and 6 pairs of doubtful ovularity. He lists some fifty conclusions from the investigations of his material. He found the personality resemblances of uniovular twins to be great. "The one feature in which a difference was often marked was in energy of character. The twin relationship itself, with its aspects of dominance and submission, appeared to favor a polar development in this respect."

He found the concordance rate of schizophrenia in uniovular twins is 76 per cent, in binovular twins 14 per cent.

His series of manic depressive psychotics is quite small. In them he finds a concordance of 50 per cent in uniovular twins and 29 per cent in binovular twins. In Kallmann's series of affective psychoses, which was much larger, he found a 96 per cent concordance in uniovular twins and 26 per cent in binovular twins. Slater's material on neurotic and psychopathic twins seems also too small for very valid conclusions. In them he finds a concordance of 25 per cent in uniovular and 19 per cent in binovular twins.

The bulk of the 385 page volume is devoted to a detailed clinical presentation of his 297 cases.

At a time when in psychiatry—particularly in American psychiatry—too little attention is being paid to heredity, this is an important contribution. It has been carried out with as great a scientific exactness as the nature of the material permits.

MANFRED S. GUTTMACHER

**Holt Pediatrics,** 12th edition. By L. EMMETT HOLT, JR. AND RUSTIN MCINTOSH. 1485 pp., $15.00. Appleton-Century-Crofts, Inc., New York.

This text, first written by Dr. L. Emmett Holt in 1896, and periodically revised thereafter by him and his successors, has long been considered the standard reference book on pediatrics. Since the appearance of the previous edition in 1940, however, such strides have been made in pediatrics and medicine in general as to outdate rapidly any text more than several years old. Consequently, several admirable texts which have appeared in the last ten years have assumed wider popularity. The present, or twelfth, edition of *Holt Pediatrics* should, however, go far to regain the preeminence previously occupied by this book.

Those familiar with previous editions will be pleased to note that the same general outline has been followed. A number of sections have undergone little or no change, but where advisable whole sections have been rewritten or expanded, and several new disease entities have been added. The number of contributors is over twice that of the previous edition, and yet uniformity has been maintained throughout by careful editing. The indications for and use of the newer antibiotics and hormonal agents are adequately covered under each specific disease. The sections on erythroblastosis fetalis, tuberculosis, prematurity, epilepsy, and genetics have been completely rewritten. Sections on new disease entities have been added, such as Coxsackie viruses, retrolental fibroplasia, hyaline membrane disease, and infantile cortical hyperostosis. Reference tables on growth, height and weight have been removed from the text to an appendix, to which have been added a valuable table on normal chemical values and a table of poisonings and their treatment. As a result of these changes, *Holt Pediatrics* is at present the most complete and up-to-date, single-volume text-book on pediatrics and may be highly recommended for the medical library of the pediatrician, practitioner or medical student.

JOHN L. PECK

**American Pocket Medical Dictionary,** 19th edition. 639 pp., $3.25 (plain) $3.75 (with thumb-index). W. B. Saunders Co., Philadelphia, Pa.

This 639 page pocket-sized dictionary is designed primarily for "students and practitioners in such fields as nursing, pharmacy, dentistry, medical technology, medical stenography, dental hygiene, veterinary science and other related disciplines." The dictionary gives short, concise definitions adequate for the population for which it is intended. Newer chemotherapeutic and hormonal preparations are described. Commonly used trade names are included, e.g. chloromycetin and chloroamphenicol are both listed. Abbreviations such as ACTH, P.M.I. and L.O.A. are defined. A great many less well-known and little used abbreviations such as H.D.R.W. (hearing distance right ear for a watch) are also included. The definitions are literal, often neglecting common medical usage. For example, this dictionary would not help the student nurse understand a physician's reference to Acid Fast Bacilli. Acid Fast is defined: not decolorized by acids. Under Bacillus we find only Koch's b., mycobacterium tuberculosis. No gross errors or omissions were detected and it may be concluded that this dictionary is adequate for the students for whom it is intended.

RICHARD S. ROSS

**Ballistocardiography: The Application of the Direct Ballistocardiograph to Clinical Medicine.** By WILLIAM DOCK, HARRY MANDELBAUM AND ROBERT A. MANDELBAUM. 293 pp., $9.50. The C. V. Mosby Co., St. Louis, Missouri.

One of the few in the relatively young field of ballistocardiography, this book by Dr. Dock and his co-authors gives, by far, the most comprehensive treatment the subject has thus far received. While many, including this reviewer, may argue that the method is too new and its principles too imperfectly understood to justify such a treatise, the authors evidently felt obliged to undertake it in the interest of practicing clinicians, who, in increasingly large numbers, have begun to use ballistocardiographic methods for patient study. In the light of their own experience, the authors have attempted to arrange and unify the facts and concepts on which ballistocardiography is based. The book is not a review of publications in the field, although it is well documented with an extensive bibliography, but is, rather, an account of conclusions reached as a result of personal observation. Written in a lucid, informal, narrative style, it is readable, though complete and detailed. There are sixteen chapters, three appendices and a profusion of illustrations. The book contains much information of value to those concerned with the recording and empirical interpretation of ballistocardiograms. There are sections on the construction, standardization and operation of direct-body ballistocardiographs, and on reading and classifying ballistocardiograms. The behavior of condensers is discussed and a calibration technique is described.

In the first chapter there is a brief and simplified description of some of the principles underlying the methods. It is pointed out that there are inherent errors in all of the current methods of recording the ballistocardiogram, these being mainly due to the body's elastic properties which tend to distort the true force "pattern". The external coupling between skeleton and supporting surface produces large errors in timing and amplitude and probably in direction. This consideration fully justifies the authors' statement that—"records of bodily motion can give only fortuitous resemblance to the actual curve of the forces being applied by the heart to the walls of the great vessels". The authors then turn their attention to the "generator" and the factors involved in cardiovascular force production. At the outset, they point out the numerous difficulties encountered in deriving a general force curve by summating the forces, varying in time, magnitude and direction, associated with various dynamic events. Nevertheless, they submit a rather detailed outline of the probable cause and direction of the principal forces responsible for the ballistocardiogram along with evidence supporting their beliefs. In later chapters dealing with clinical application, the various types of waveform abnormality are related to changes in force production resulting from

specific functional and anatomical abnormalities of the cardiovascular system. Thus, the authors have attempted to give physiological meaning to empirical ballistocardiographic observations. This goal is of undisputed importance, but such correlations based on current knowledge tend to tie empirical observations to speculative and dimly perceived physiological mechanisms. Lack of information concerning force production and transmission, in normal and disease states, remains the greatest challenge in the field. It should be fully recognized that there is very little factual data on which to base close relationships between ballistic events and details of cardiovascular activity. Many of the speculations voiced in past years with regard to mechanism and causality have, by frequent repetition, come to assume the solidity of fact. There can be no real objection to the authors' attempts at formulating a concept of causality for the ballistocardiogram provided those new to the field do not mistake it for fact. Unfortunately, on far too many occasions the authors failed to point out this distinction.

The clinical section of the book is quite complete and covers essentially all of the disease states of interest to the ballistocardiographer. For the most part, it deals with the clinical application of the ballistocardiograph; relationship of the wave form to anatomical and functional abnormalities, use of the method in evaluating clinical course and prognosis, value in diagnosis, etc. The presentation takes the form of rather general conclusions based on the authors' results and illustrated by a large number of individual case presentations. There is a noticeable absence, however, of compilations of data from which these conclusions were drawn. While this undoubtedly makes for easier reading, the reader is not supplied with the information which would allow him to draw his own conclusions. The textual material is excellent in those sections wherein the authors have confined themselves to the running narrative of factual reporting but is often weakened by conclusions arrived at through tenuous argument or intuitive reasoning.

While this reviewer can agree with many of the conclusions drawn by the authors in this book, there are also a number with which he strongly disagrees. The issue on which Dr. Dock and his co-workers are most susceptible to serious criticism concerns the significance of the abnormal ballistocardiograms observed in about half of the asymptomatic, clinically normal persons above the age of 45 or 50. The authors contend that, in the majority of cases, these abnormalities are due to myocardial scars resulting from coronary artery disease. There is still no undeniable proof for this contention and the evidence in its support is largely circumstantial. One must conclude, therefore, that currently available data are not sufficient to allow a final decision on the clinical meaning of these abnormal records. Until it can be stated with certainty that these are due to coronary artery disease alone, it would seem the wisest course to suspend judgment on them. Perhaps the wisest statement made by the authors and one which deserves emphasis here was, "The electrocardiograph has in many instances resulted in more harm than benefit to the patient and the ballistocardiograph, because it is more sensitive, may be subject to even worse abuse."

The reader may or may not accept the contentions set forth in this book but he cannot fail to find it stimulating and provocative.

WILLIAM R. SCARBOROUGH

**Sympathetic Control of Human Blood Vessels.** By H. BARCROFT AND H. J. C. SWAN. 165 pp., $3.75. The Williams & Wilkins Co., Baltimore, Md.

The work described in this little volume is an excellent example of simple but informative experiments, in the design of which British clinical physiologists are masters. It is, furthermore, an example of the lucid reporting at which our British colleagues are likewise so skilful. The book has as much to recommend it as a model for experimental design and scientific

communication as it does for the factual material it presents. For the sake of those interested particularly in the last, the following topics discussed by the authors are listed: Sympathetic vasoconstrictor and vasodilator nerves to skeletal muscle; the action of adrenaline and of noradrenaline on the circulation in skeletal muscle in the skin, and in the general circulation in skeletal muscle during exercise; effects of sympathetic denervation and of adrenergic blockade; physiologic effects of pheochromocytomas; fainting. Appended to the main presentation is an interesting and instructive, historical and technical discussion of plethysmography, the principal technique employed in the experiments described.

VICTOR A. MCKUSICK

**The Team Plan: A Manual for Nursing Service.** By DOROTHY PERKINS NEWCOMB. 82 pp., $1.50. G. P. Putnam's Sons, New York.

This small book reviews an experiment in the Massachusetts General Hospital which arose out of the concern of a nursing service administrator and her staff to provide adequate nursing care for patients. The primary objective of the team plan is to coordinate the skills of professional nurses, student nurses, and nonprofessional workers to improve patient care. The plan, in use in many hospitals, is neither new nor original with the author, but this manual has the advantage of presenting in a concise fashion methods of administering the team plan. After discussing the advantages of the team plan and the philosophy underlying it, to assure that all patients receive professional or professionally-directed care, the author explains such practical points as the organization of the team, selection of team members, and assignment of patient care. Though the book describes a situation in one hospital, the techniques of instituting and carrying out the team plan should be adaptable to many situations.

The book is written in a readable fashion. Diagrams and a reference list are included.

MARGARET E. COURTNEY

**Rehabilitation of the Physically Handicapped.** By HENRY H. KESSLER. 275 pp., $4.00. Columbia University Press, New York.

Although Dr. Kessler's book seems to have been written chiefly for the general public, physicians who have not yet had experience in the field of rehabilitation will find it informative and, depending on the intensity and direction of their prejudices, pleasant reading. Dr. Kessler, a pioneer in this country in his field, writes clearly and forcefully and, like many good pioneers, with dedication to his subject.

Rehabilitation, or the art of training the individual to make the best use of his physical capacities, requires in its full sense, integrated resources of the physician, physical therapist, vocational counselor and social worker and it enters, therefore, the field of social sciences. Dr. Kessler presents the broad approach and it is inevitable that a good deal of it is a matter of opinion.

A large scale rehabilitation program is expensive. Its proponents argue that it pays for itself many times over by creating wage-earners or by releasing wage-earners from the burden of caring for a handicapped member of the household. Difficulties in validating this sort of argument are apparent and although Dr. Kessler does offer support for them, whether they are convincing or not need not be crucial. It may be that no more than intuition and good will are necessary for acceptance of the worth of a solid rehabilitation program. Dr. Kessler has these and does a fine job of impressing them upon the reader.

K. L. ZIERLER

**Clinical Diagnosis by Laboratory Methods,** 12th edition. By JAMES CAMPBELL TODD, ARTHUR HAWLEY SANFORD AND BENJAMIN B. WELLS, 998 pp., $8.50. W. B. Saunders Co., Philadelphia, Pa.

This standard text promises, in its preface, no drastic changes from the Eleventh Edition (of 1948) and none are found. Very few of the chapter-end references bear a later date. That is regrettable, for there *have* been changes in laboratory methods through the past five years—and one's old stand-bys should keep up-to-date. The volume's chief asset continues to be the wealth of very practical advice and laboratory know-how in the technical portions.

More recent are sections or parts of sections on urine, blood and clinical chemistry. Bacteriologic nomenclature was brought up to date. Somewhat out of proportion in space, the chapter on the Serologic Test for Syphilis is given one hundred pages and is quite repetitious in detail. It conforms to the Public Health Service techniques and standards. Little is made of biologic false positives and the TPI is not mentioned. The colloidal gold test is fully explained and the three types of positive curves are still specified.

Without detailing the many techniques developed or popularized since 1948 that one would like included, some of the shorter chapters could well have been abandoned. The one on antibiotics discusses penicillin and gives an early method of sensitivity testing. Then one, seven-line paragraph mentions streptomycin, chloromycetin, aureomycin, "and other similar antibiotics".

Illustrations are numerous, 946 with 197 in color. These are generally well chosen and printed, particularly the newer material. Some of the 'old retainers' are as vague as ever. An occasional instrument seems more of a museum piece than part of a practical book.

A short Appendix details such staining solutions as are not given in the text. There is an Index-Outline of Laboratory Findings in Important Diseases. The general Index is adequate, with italics for pages with illustrations where they occur.

This volume continues to survey a wide field and is in simple, elemental terms, with adequate definitions, easily understood by beginners. It can be recommended to students and technicians as an excellent book with which to work.

CONRAD ACTON

**Basic Medical Physiology.** By W. B. YOUMANS. 436 pp., $7.50. Year Book Publshers, Chicago, Ill.

The avowed object of this book is to present concisely the essential background on which to build more detailed knowledge of preclinical physiology. The author's aim was to achieve brevity by presenting the "current state of information without giving detailed evidence and without discussing the historical background." The result of this approach is a dull book of doubtful value. In no sense is the book recommended as an introduction to physiology. It is too condensed and synoptic to be likely to stimulate interest in the subject, and interest is an important condition for learning and understanding. At best it may be considered as a bland diet for those who are suffering from pre-examination mental indigestion. It is not, however, a wholesome diet for purposes of long term mental nutrition. It does not present a satisfactory core of hard fact on which to build, but meagre as is its content, it includes a number of moot points without needed qualifications. It contains much that, in Howell's words, "represents the uncertain compromises of past generations" endowed with a fictitious air of validity because they have been carried through many editions of textbooks, for example, the Bainbridge reflex, and Douglas and Haldane's much too beautiful diagram (1909) of alveolar gas tensions in apnoea. Somewhat newer errors include the statement that the disturbances in adrenal insufficiency are related in part to an increased per-

meability of the cell membranes to Na and K. More important, however, than specific error is the general tone, which is that of presenting current concepts in an oversimplified and didactic manner, without giving enough specific information to permit a development of that degree of thoughtful understanding which is necessary if a student is going to evaluate and make use of concepts.

EVELYN HOWARD

## BOOKS RECEIVED FOR REVIEW

**Hunted Heretic. The Life and Death of Servetus.** By ROLAND H. BAINTON. 270 pp., $3.75. The Beacon Press, Boston, Mass.

**Lehrbuch der Klinischen Hämatologie.** By HANS SCHULTEN. 508 pp., Ganzleinen DM 54. Georg Thieme Verlag, Stuttgart, Germany.

**Physiology of the Eye. Clinical Application.** By FRANCIS HEED ADLER. 734 pp., $13.00. The C. V. Mosby Co., St. Louis, Missouri.

**The Unique Influence of the Johns Hopkins University on American Medicine.** By RICHARD HARRISON SHRYOCK. 77 pp., Danish kr. 14.00 (bound) ($2.18). Ejnar Munksgaard, Copenhagen, Denmark.